THE EFFECT OF 24-HOUR INTRAOCULAR PRESSURE FLUCTUATION ON GLAUCOMA PROGRESSION IN PRIMARY ANGLE CLOSURE GLAUCOMA

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

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TABLE OF CONTENTS Page

LIST OF TABLES

LIST OF FIGURES

ABSTRAK

Tajuk

Kajian 24-Jam Fluktuasi Tekanan Mata dalam Glaukoma Primer Sudut Tertutup Maju dan Tidak Maju

Pendahuluan

Glaukoma Primer Sudut Tertutup (GPST) merupakan penyakit yang kerap didiagnosa di kalangan populasi Asia. Bangsa Melayu adalah antara kaum yang dikenalpasti menghidapi GPST dengan prevalens sebanyak 0.12% hingga 2.5%. Sehingga kini, tekanan mata adalah satu-satunya risiko faktor yang boleh dikawal. Dua subkomponen tekanan mata iaitu purata nilai tekanan mata yang tinggi dan nilai jurang turun naik tekanan mata yang luas merupakan faktor penting penyebab kemajuan GPST.

Objektif

Mengenalpasti dan membandingkan purata nilai purata tekanan mata, nilai puncak, nilai dasar, dan nilai turun naik dalam masa 24 jam, di kalangan mata GPST maju dan tidak maju.

Metodologi

Satu kajian keratan rentas telah dijalankan di Hospital Universiti Sains Malaysia, Kelantan yang mana melibatkan seramai 25 pesakit dengan 50 mata yang telah didiagnosa GPST. Mereka dibahagikan kepada 2 kumpulan iaitu mata maju dan mata tidak maju. Kesemua mereka dimasukkan ke dalam wad selama 24 jam. Tekanan mata diukur sebanyak 6 kali selang masa 4 jam, iaitu pada 0800, 1200, 1600, 2000, 2400, dan 0400. Tonometer Aplanasi Goldmann digunakan untuk semua pengukuran tekanan mata. Analisis statistik yang digunakan adalah ujian 'independent t', ujian 'Mann-Whitney U', dan ujian 'Fisher's exact'.

Keputusan

Keputusan kajian mendapati bahawa majoriti dari kumpulan mata GPST maju menunjukkan nilai tekanan mata puncak pada sebelah malam dengan nilai tekanan mata dasar pada sebelah petang, manakala kumpulan mata tidak maju menunjukkan nilai tekanan mata puncak pada sebelah pagi dan nilai tekanan mata dasar pada sebelah malam. Pada selang masa 4 jam, kumpulan mata maju mempunyai nilai purata tekanan mata, nilai puncak, dan nilai dasar yang lebih rendah tetapi jurang nilai turun naik yang lebih luas. Dalam masa 24 jam, tiada perbezaan yang signifikan pada semua variasi tekanan mata. Keseluruhannya, julat nilai purata tekanan mata adalah antara 13.7 ke 15.3 mmHg ($p = 0.202$), julat nilai purata tekanan mata puncak adalah antara 17.0 ke 18.0 mmHg ($p = 0.285$), julat nilai purata tekanan mata dasar adalah antara 11.0 ke 13.0 mmHg ($p = 0.151$), dan julat nilai turun naik tekanan mata adalah 6.0 mmHg ($p = 0.803$).

Kesimpulan

Hasil kajian menunjukkan tiada perbezaan yang signifikan pada semua variasi tekanan mata dalam masa 24 jam dalam kedua-dua kumpulan mata GPST maju dan tidak maju. Walaupun julat nilai turun naik tekanan mata adalah sama dalam masa 24 jam, kumpulan mata maju menunjukkan jurang nilai turun naik tekanan mata yang lebih luas pada selang masa 4 jam.

ABSTRACT

Title

The Effect of 24-Hour Intraocular Pressure Fluctuation on Glaucoma Progression in Primary Angle Closure Glaucoma

Introduction

Primary Angle Closure Glaucoma (PACG) is a common glaucoma type in Asian population. Malays are among affected races in South East Asian with PACG prevalence of 0.12% to 2.5%. To date, intraocular pressure (IOP) is the only modifiable glaucoma risk factor. Two IOP subcomponents; the higher mean IOP and the wider IOP fluctuations are currently being looked upon as important predictors of glaucoma progression.

Objectives

To determine and compare the 24-hour overall mean IOP, mean IOP peak, mean IOP trough, and IOP fluctuation in progressed and non-progressed PACG.

Methodology

A cross-sectional study was conducted in Hospital Universiti Sains Malaysia, Kelantan involving 25 patients with 50 eyes diagnosed with PACG. They were grouped into progressed PACG (11 eyes) and non-progressed PACG (39 eyes). AGIS scoring system was used to determine the progression group. All patients were admitted for 24 hours period. Six IOP measurements were performed at 4-hour time points; at 0800, 1200, 1600, 2000, 2400, and 0400. Goldmann Applanation Tonometer (GAT) was used for all IOP measurements. Statistical analysis used were independent t test, Mann-Whitney U test, and Fisher's exact test.

Results

Majority of progressed eye group of PACG exhibited patterns of night peak with afternoon trough, while non-progressed eye group showed patterns of morning peak with night trough. At 4-hour time points, the progressed eye group had lower mean IOP, mean peak IOP, and mean trough IOP but wider mean IOP fluctuation. Over 24 hour period, there was no significant difference for all IOP variables in both groups. The 24-hour mean overall IOP mean range was 13.7 to 15.3 mmHg ($p = 0.202$), overall mean IOP peak range was 17.0 to 18.0 mmHg ($p = 0.285$), overall mean trough range was 11.0 to 13.0 mmHg ($p = 0.151$), and overall mean IOP fluctuation was 6.0 mmHg ($p = 0.803$).

Conclusion

Progressed and non-progressed eye group of PACG demonstrated no significant difference in terms of all IOP variables over 24-hour period. Despite similar overall mean IOP fluctuation during 24-hour period, the progressed eye group had wider mean IOP fluctuation than the non-progressed eye group at 4-hour time points.

CHAPTER 1
INTRODUCTION

1.0 INTRODUCTION

1.1 Glaucoma

Glaucoma is a progressive optic neuropathy disease with blinding potential. It commonly refers to a group of disorders that exhibit optic nerve head cupping and characteristic visual field loss. Glaucoma in Greek means clouded or blue-green hue, which Hippocrates first used to describe blindness in advanced years associated with pupil's glazed appearance (Fronimopoulos & Lascaratos, 1991).

The understanding of pathogenesis of glaucoma involves 2 theories; mechanical and vascular mechanism. These 2 concepts were introduced in mid-nineteenth century. Muller suggested the mechanical theory in 1858, while von Jeager proposed the vascular theory in the same year (Pinazo-Duran *et al.*, 2011). Elevated IOP is responsible for optic nerve compression and death of the neurons in the mechanical mechanism, where as vascular dysregulation affecting ocular perfusion pressure that leads to optic atrophy is postulated to play the main role in the vascular mechanism. Both eventually share common final sequel: progressive visual field defect hence blindness.

Global impact of glaucoma is devastating. It is costly from both human and economic perspectives. Glaucoma affects quality of vision as well as quality of life. WHO demonstrated that approximately 5.2 million blindness attributable to glaucoma, which represented 15% of total burden of world blindness (Thylefors and

Negrel, 1994). In Malaysia, glaucoma emerged as the fifth leading cause of blindness and low vision according to National Eye Survey 1996 (Zainal *et al.*, 2002). Local survey showed that it was the second leading cause of blindness in urban population after cataract (Reddy *et al.*, 2008). In other South East Asia countries, glaucoma is the second cause of blindness in China, Thailand and Singapore, and the third cause of blindness in Philippines (Rojanapongpun, 2005).

Visual impairment secondary to glaucoma may cause difficulties in mobility, driving and social interactions (Coleman, 1999). Glaucoma patients are also likely at higher risk to involve in motor vehicle collision owing to their restricted visual field (McGwin *et al.*, 2005). Blind glaucoma patients are dependent of activity daily living, thus contribute further to burden people around them, especially the family and relatives. In terms of nation economic burden, cost effectiveness on medications and surgeries is among the issues apart from expenditures spent on regular visits monitoring and compliance, screening and investigation tools purchases, and losing human resource from blindness.

WHO has classified glaucoma into 3 groups: congenital (genetic or development), primary glaucoma (open angle or angle closure), and secondary glaucoma. All these have different etiologies and course of treatment. Worldwide, the distribution of PACG and POAG is both geographically and ethnically variable. PACG is common in Asia, while POAG predominates in other parts of continents. PACG was estimated to blind more people than POAG (Foster *et al.*, 2000).

Despite the alarming figures of glaucoma cases observed each year, the vision loss usually can be delayed with early detection and appropriate management. Factors influencing the increase in glaucoma prevalence are varied and not been fully understood. Among these, IOP remains the most prominent and consistent glaucoma risk factor as concluded by 4 major studies: Ocular Hypertension Treatment Study (OHTS), Early Manifest Glaucoma Trial (EMGT), Advanced Glaucoma Intervention Study (AGIS), and Collaborative Normal Tension Glaucoma Study (CNTG) (Coleman *et al.*, 2004; Bengtsson *et al.*, 2007; Caprioli & Coleman, 2008; Anderson, 2003).

As it is the only modifiable risk factor, lowering IOP has been a mainstay focus of glaucoma treatment, either by pharmacologically, or surgically, or both. The results of the AGIS have proven that lowering IOP prevents further optic nerve damage by maintaining targeted average IOP 12-14 mmHg, as signified by no visual field progression over the 7 years course compared to those who had higher IOP. But keeping IOP at low level is just inadequate. There is other issue beyond the target IOP level to answer why many patients still progress despite achieved target IOP at intervisits. The idea of "IOP stability" concept hence was introduced and frequently emphasized in current studies. Two IOP subcomponent; the mean IOP and IOP fluctuations are now being looked upon as another important predictors of glaucoma progression. Therefore, stabilizing both parameters need to be included and tailored in the management strategy (Asrani *et al.*, 2000; Singh & Shrivastava, 2009).

1.2 Angle Closure Glaucoma

1.2.1 Epidemiology of Angle Closure Glaucoma

WHO data in 1993 shows that about 23 million individuals had confirmed glaucoma while glaucoma suspects reached around 105 million persons. Out of this figure, POAG affects 13.5 million cases and PACG accounts for 6 million people, both seen in subjects over age 40 (Thylefors & Negrel, 1994). The prevalence of glaucoma is increasing and by year 2020, an estimated 79.6 million people worldwide are expected to develop glaucoma (Quigley & Broman, 2006). Population-based data from South East Asia Glaucoma Interest Group Meeting (SEAGIG 2004) showed POAG has higher rate than PACG in Malaysia, Singapore and Thailand, with reverse order for Philippines (Rojanapongpun, 2005). However data for PACG in Asia have increased in past few years (See *et al.*, 2011). Cedrone and colleague analyzed a series of 56 studies on glaucoma prevalence, and concluded that PACG is commonest among Asian ethnic groups whereas POAG is more common in African origin and white population (Cedrone *et al.*, 2008). In Malaysia, ratio of POAG to PACG was approximately 1.5:1.0 (Rojanapongpun, 2005). Prevalence of PACG in adult Asians was 0.75% and more than half of them were female (Cheng *et al.*, 2014). It increases with age (Foster et al., 2000). Malays are among affected races in South East Asian with PACG prevalence of 0.12% to 2.5% (Shen *et al.*, 2009; Bourne *et al.*, 2003; Casson *et al.*, 2007). In a hospital-based study in Malaysia, the prevalence of PACG was once reported 30.0% and the incidence of PACG was once reported 0.86% with Malays accounted one third of the 3 major races (Selvarajah, 1998).

1.2.2 Classification of Angle Closure

According to International Society Geographical & Epidemiological Ophthalmology definition, glaucoma with angle closure is classified and staged into Primary Angle Closure Suspect (PACS), Primary Angle Closure (PAC), and Primary Angle Closure Glaucoma (PACG). In PACS, narrow angle is the only abnormality present. It may progress to PAC with manifested high IOP and other findings, but without glaucomatous optic disc changes. PACG hence, reserved for PAC in presence of glaucomatous optic neuropathy with or without visual field loss (Foster *et al.*, 2002).

1.2.3 Mechanism of Angle Closure

There are 4 main mechanisms of angle closure, each of which may co-exist with another: pupil-block (block at level of iris), anterior non pupil-block that includes plateau iris (block at level of ciliary body), lens-related (block at level of lens), and retrolenticular (block posterior to lens) (Ritch & Lowe, 1996). Identifying mechanism responsible for angle closure is important in addition to establish the disease stage. It is helpful in guiding the appropriate choice of treatment. The two schemes (staging and mechanism) therefore should be used in parallel when managing an angle closure case.

1.2.3.1 Assessment of anterior chamber depth

Anterior chamber depth can be assessed qualitatively using Smith's method and Van Herrick's method. Both use slit lamp biomicroscope. Smith's method estimates the central anterior chamber depth, while Van Herrick's method approximates the peripheral (Smith, 1979; Van Herick *et al.*, 1969). Another method of assessment is by using A-scan, which is quantitative.

1.2.3.2 Assessment of anterior chamber angle

Gonioscopy is the commonest procedure in assessing anterior chamber angle. It uses contact goniolens together with slit lamp biomicroscope. The angle was subsequently graded using Shaffer system, which consists of 5 grades from 0 to 4 (Fellman *et al.*, 2012). Apart from gonioscopy, cross-sectional images of anterior chamber structures, specifically the angles also can be generated using Optical Coherence Tomography (OCT) and Oculus Pentacam. These images can be used to take measurements of the angle.

1.2.4 Risk factors of Angle Closure Glaucoma

Assessing risk factors in a potential angle closure glaucoma patient is essential. Mass screening can be narrowed down to a selected population. It also aids in predicting the incidence of acute attack and long-term glaucoma progression. Ocular biometry risk factors are narrow drainage angles, shorter axial length, shallow anterior chamber depth, lens thickness and position, and thicker iris. Meanwhile, the systemic

risk factors include age of 40 years and above, female gender, ethnicity of Inuit or East Asian, genetic, and environmental such as climate monsoon (Ameraginghe, 2008) (Ch'ng *et al.*, 2013). Amongst these, shallow anterior chamber depth is the leading anatomical risk factor with Chinese ethnicity has the most significant anterior chamber and angle anatomy difference.

1.2.5 Clinical Presentation of Angle Closure Glaucoma

Classic acute primary angle closure (APAC) episode usually brought patient earlier to ophthalmologist due to intolerable eye pain and worsened vision. In such case, IOP reading almost always high and complicated with injected conjunctiva, epithelial edema, shallow anterior chamber, mid-dilated pupil, iris ischemia, and hazy fundal view. However, it is also not uncommon to diagnose cases of advanced PACG at first visit. Painless typical glaucomatous visual field loss and characteristic glaucomatous disc cupping are the common late signs. Nevertheless, both acute and chronic stages are often seen overlapping in the clinical presentation.

1.2.6 Management of Angle Closure Glaucoma

Diagnosis of angle closure glaucoma is mainly clinical and should be made with careful slit lamp examination, which include IOP measurement and gonioscopy. Further investigations may be required such as visual field, ultrasound biomicroscopy, optic nerve head analysis by optical coherence tomography, and central cornea thickness. The aim of treating PAC and PACG is to eliminate the underlying pathophysiological mechanism and to reduce IOP. This can be achieved

medically and/or surgically. Medical treatment consists of laser peripheral iridotomy or iridoplasty, and IOP lowering agents that can be delivered topically, per oral or intravenous. They are available from classes of beta blocker, adrenergic agonist, prostaglandin analog, carbonic anhydrase inhibitor, parasympathomimetic, fixed combination medications, and hyperosmotic agents. Surgically, options include trabeculectomy, lens extraction, combined lens extraction with trabeculectomy, and glaucoma drainage device implantation (See *et al.*, 2011). In case of acute PAC, rapid IOP reduction and control is needed to limit optic nerve insult, hence preventing long-term glaucoma progression.

1.3 Intraocular Pressure

1.3.1 Concept of Normal Intraocular Pressure

Intraocular pressure is determined by balance between aqueous production and outflow. Goldmann equation clearly described the relationship between the IOP and the components of aqueous humor dynamics: Po = (F/C) + Pv ; Po is the IOP in millimeters of mercury (mmHg), F is the rate of aqueous formation, C is the facility of outflow, and Pv is the episcleral venous pressure (American Aceademy of Ophthalmology, 2011). Mean IOP of 15.5 mmHg, with a standard deviation of 2.6 mmHg have been reported in large-scale population-based epidemiologic studies. Therefore “normal” IOP is defined as 2 standard deviations above or below the mean IOP, or approximately 10-21 mmHg. IOP of outside this range is considered pathological and abnormal (Alimuddin, 1956).

1.3.1.1 Aqueous humour formation

There are two steps of aqueous humour production. Firstly, plasma filtrate is formed within the stroma of ciliary body. Secondly, aqueous humour is formed from this filtrate across the blood-aqueous barrier. The aqueous humour subsequently secreted into posterior chamber through two mechanisms, in which active secretion predominates than passive secretion. Active secretion by non-pigmented ciliary epithelium involves metabolic process that is Na+/K+ ATPase pump dependent, whereas passive secretion by ultrafiltration and diffusion are dependent on capillary hydrostatic pressure, oncotic pressure and IOP level (Kanski & Bowling, 2011)

1.3.1.2 Aqueous humour outflow

Aqueous humour flows from the posterior chamber into the anterior chamber via pupil. From there, it exits the eye by two different routes, either through trabecular or uveoscleral. Trabecular route is also known as conventional route as it accounts for approximately 90% of aqueous outflow. From trabecular, aqueous humour then enters Schlemm canal and is subsequently drained by episcleral veins. The remaining 10% will be channeled into uveoscleral route (Kanski & Bowling, 2011).

1.3.2 Measurement of Intraocular Pressure

IOP in general, is indirectly calculated by measuring the amount of force that is required to flatten a section of cornea. Various IOP measurement tools have been developed over decades. Basically, there are 4 types of tonometry available to date: applanation tonometry (Goldmann tonometry, Perkins tonometry, Ocular Response Analyzer, air puff tonometry), indentation tonometry (Schiotz tonometer, Pneumotonometer, Tono-Pen), rebound tonometry (ICare), and Pascal Dynamic Contour Tonometer. Amongst these, Goldmann applanation tonometry remains a gold standard in IOP taking, despite its shortage on numerous ocular biomechanical factors that can erroneously lead to overestimation or underestimation of IOP measurement. Furthermore, it is known that repeated applanation testing using Goldmann-type tonometers might decrease IOP in ipsilateral eye, which cannot fully be explained (Moses, 1961). With emergence of newer inventions, IOP measurements are no longer affected by ocular biomechanical properties that are significant in Goldmann tonometry measurement. Recent development of more

advanced invention using contact lens sensor (SENSIMED Triggerfish), allows short-term reproducibility of continuous 24-hour IOP monitoring (Mansouri *et al.*, 2012). Studies on this device are currently on going in evaluating its clinical safety, tolerability and efficacy.

1.3.3 Factors Affecting Intraocular Pressure Measurement Accuracy

IOP measurements in clinical setting may be affected by numerous ocular biomechanical factors of cornea and tear film such as central cornea thickness, cornea curvature, corneal rigidity and hydration, cornea scarring, thin or thick of tear film (Whitacre & Stein, 1993). False elevated IOP reading may be contributed mechanically such as pressure from a finger on the eyelid while taking the measurement, in squeezed eyes, breath holding and Valsalva maneuver by the patient during measurement. The choice of IOP measurement tools hence needs consideration in different situations.

1.3.4 Goldmann Applanation Tonometer

Goldmann Applanation Tonometer (GAT) is the gold standard of IOP measurement. It requires fluorescein dye to highlight tear film. The force of flattening cornea area of 3.06 mm diameter is measured. The tonometer uses split-imaged prism that generates image of tear meniscus, which divides into superior and inferior arc. When both arcs are aligned in such that their inner margins just touch, IOP is taken. As wide contact surface area is needed for the measurement with fluorescein dye, local

anesthetic eye drop is essential for patient's comfort. GAT needs calibration at frequent interval.

1.3.5 Intraocular Pressure Circadian Rhythm in Primary Angle Closure Glaucoma

Many agreed that IOP fluctuate in rhythmical circadian pattern and eyes with glaucoma were observed to have greater fluctuation. Circadian rhythm of IOP comprises the diurnal and nocturnal curves. Pattern of IOP diurnal curve varies in different types of glaucoma (Wilensky, 1991). IOP circadian rhythm in PACG has been compared to POAG and normal eyes over 24-hour period in few studies. In PACG, documented average IOP peak was 25 mmHg, range of IOP was 12-32 mmHg, and diurnal fluctuation was 6-8 mmHg (Sihota *et al.*, 2005). The 3 parameters did not significantly differ when comparing PACG to POAG, however significant lower values were observed in normal eyes. In PACG and PAC eyes, higher diurnal IOP fluctuation of 4-5 mmHg has been observed in comparison to PACS patients and normal controls (Baskaran *et al.*, 2009). In PACG, IOP peak was observed not only in afternoon, but also at night or early morning, midnight and morning (Sihota *et al*, 2005; Leydhecker, 1976; Shapiro & Zauberman, 1979). Greater IOP dependence was observed for optic nerve damage in PACG than POAG (Gazzard *et al.*, 2003). A diurnal fluctuation of more than 6 mmHg with IOP 21 mmHg was never seen in normal eyes and should be considered pathological if present.

1.3.6 Factors Affecting Intraocular Pressure Fluctuation

IOP physiologically is in a state of flux and therefore it varies in short and long term (Kirstein *et al.*, 2011). There are many factors affecting physiological IOP, and this may exaggerate in glaucoma individuals. Diurnal variation is one of many other factors contributing to short-term fluctuations, apart from body posture, exercise, eye movements, Valsalva maneuvers and various food or drugs consumption. IOP has been observed to have nocturnal variation (Liu, 1998) and most IOP peaks occur outside office hours (Mosaed, 2005). Postural changes have significant effect on IOP (Bill, 1978; Baskaran *et al.*, 2006). On the other hand, long-term fluctuations have been associated with advanced age, season, diet, systemic blood pressure, race, ethnic origin, and body weight. Persistent accumulative short-term variation may lead to long-term fluctuation. It is believed that long-term fluctuation of IOP may be a risk factor for glaucoma progression (Bergea *et al.*, 1999; Asrani *et al.*, 2000; Nouri-Madhavi *et al.*, 2004).

1.3.7 Role of Intraocular Pressure Fluctuation in Glaucoma Progression

At present, recent data suggests that there are more risk factors to consider in glaucoma rather than IOP measurement taken in clinic during office-hour visit. Being an inconstant value, IOP varies considerably and respond to short as well as long-term influences. Despite that, a pattern to IOP variation over 24 hours course seems to be observed in which a given individual has reasonable amount of consistency and reproducibility (Wilensky, 1991). Other diurnal variation in the

body, such as cortisol production, was thought to be related to this pattern (Schwartz, 1966).

Role of 24-hour IOP, thus control plays an important aspect in glaucoma management. Its implication as a risk for progression demonstrated by fluctuation as observed in many published studies. IOP fluctuations have been shown to increase risk of visual field progression in treated eyes (Asrani *et al.*, 2000). AGIS reported that over 7 years, IOP fluctuation of 1 mm Hg increased risk of progression by 30% (Nouri-Mahdavi *et al.*, 2004). Diurnal and nocturnal IOP measured in habitual position provide new insights, although accuracy of measurement technique made is questionable. Treatments have different effects on diurnal and nocturnal IOP. Newest class of glaucoma medications; the prostaglandin analogues, claimed medically lower the IOP, and stabilize the IOP circadian rhythm at the same time. Studies on 24-hour and nocturnal efficacy of glaucoma medications are ongoing (Orzalesi *et al.*, 2000; Liu *et al.*, 1999; Sit *et al.*, 2006; Liu *et al.*, 2005). Current 24-hour IOP monitoring in sleep laboratory is a research tool. Clinical practical 24-hour monitoring of IOP could increase our ability to understand glaucoma progression and its treatment effects.

1.3.8 Monitoring of Intraocular Pressure Fluctuation

There are several indications where 24-hour IOP measurement should be evaluated: in glaucomatous patients with progressive damage whenever single IOP reading is within ‘normal’ range; in patients with ocular hypertension where baseline IOP levels is required to monitor the condition; and in cases where incidental suspicious glaucomatous disc without apparent IOP elevation (David *et al.*, 1992).

1.4 Rationale Of Study

Glaucoma is an unpreventable disease of occurrence, whereby management is aimed to delay and retard its progression. As IOP is the known modifiable risk factor, reducing it has become our mainstay focus of treatment. Wide IOP fluctuation has been demonstrated to be a risk of glaucoma progression. Hence it is essential to determine and compare pattern of 24-hour IOP fluctuation in PACG patients in our local population thus its effect on visual field progression within both groups. This study hopefully will provide an insight on strategizing an aggressive target on lowering mean intraocular pressure, thus potentially minimize and narrow the intraocular fluctuation at identified specific hour.

CHAPTER 2
STUDY OBJECTIVES

2.0 STUDY OBJECTIVES

2.1 General Objectives Of This Study

To study the pattern of 24-hour intraocular pressure fluctuation in primary angle closure glaucoma patients.

2.2 Specific Objectives Of This Study

1. To determine the 24-hour overall mean intraocular pressure, overall intraocular pressure mean peak, overall intraocular pressure mean trough, and overall intraocular pressure fluctuation in progressed eye group of PACG

2. To determine the 24-hour overall mean intraocular pressure, overall intraocular pressure mean peak, overall intraocular pressure mean trough, and overall intraocular pressure fluctuation in non-progressed eye group of PACG

3. To compare the 24-hour overall mean intraocular pressure, overall intraocular pressure mean peak, overall intraocular pressure mean trough, and overall intraocular pressure fluctuation between progressed and non-progressed eye group of PACG

CHAPTER 3
METHODOLOGY

3.0 METHODOLOGY

3.1 Study Design

This is a comparative cross sectional study.

3.2 Research Setting

3.2.1 Study Research Population: Patients diagnosed with PACG, attending regular visits in Ophthalmology Clinic, Hospital Universiti Sains Malaysia

3.2.2 Period of Study : May 2012 till May 2014

3.2.3 Place of Study : 1. Ophthalmology Clinic, Hospital Universiti Sains Malaysia
2. Ophthalmology Ward, 2 Utara, Hospital Universiti Sains Malaysia

3.3 Sampling And Sample Size

3.3.1 Sampling Method

PACG patients in HUSM who fulfilled inclusion criteria and consented to participate in the study were recruited.

3.3.2 Sample Size

Sample size was calculated using PS ("Power and Sample Size") software, version 3.0.43 . t-test formula with independent design was applied.

α : level of significance

SD or σ : standard deviation of mean IOP

DD or δ = the smallest, clinically meaningful difference in mean IOP that is desired to be detected

m : ratio between progress and stable

n : sample size

$\alpha = 0.05$

Power of study = 0.8

SD or $\sigma = 1.24$ (reference: Baskaran *et al.*, 2009)

DD or $\delta = 1.0$

$m = 1$

$n = 25$

n + 10% (expected dropout) = 25 + 3

Total of 28 eyes per arm are required for this study

Total of 56 eyes are required for this study

3.4 Selection Criteria

3.4.1 Inclusion Criteria

i) Age more than 40

ii) Patients with established diagnosis of PACG

iii) At least 2 years of glaucoma clinic follow-up

3.4.2 Exclusion Criteria

i) History of penetrating keratoplasty or filtering surgery

ii) History of cataract surgery within previous 6 months

iii) Patients with secondary glaucoma and glaucoma suspect

iv) Very advanced stage of glaucoma (based on AGIS score)

v) History of severe dry eye syndrome, recurrent corneal epithelial erosion, delayed cornea wound healing, active keratitis or conjunctivitis

vi) BCVA 3/60 and worse

3.5 Ethical Approval

This study received approval from the Research Ethics Committee (Human), School of Medical Sciences, Universiti Sains Malaysia Health Campus. The research protocol adhered to the provision of the Declaration of Helsinki for research involving human subjects.

3.6 Financial Support

This study was supported by the Universiti Sains Malaysia grant. The research short term grant (account number 304/PPSP/61313008) was approved by Timbalan Naib Canselor (Penyelidikan dan Inovasi), Universiti Sains Malaysia.

3.7 Definition Of Terms

3.7.1 Primary Angle Closure Suspect (PACS)

PACS is the initial event that may progress to PAC and subsequently to PACG. There is narrow angle, in the absence of other abnormality. Narrow angle is evidenced on indentation gonioscopy by inability to see posterior (pigmented) trabecular meshwork angled 180^0 to 270^0, which is due to appositional contact between peripheral iris and the posterior trabecular meshwork (Foster *et al.*, 2002; Aung, 2005).

3.7.2 Primary Angle Closure (PAC)

In PAC, the narrow angle is present in combination with consequence of angle closure process such as peripheral anterior synechiae and/or IOP rise. IOP is raised as a result of closure of the narrow angle, and is defined as >2 standard deviations above norm for studied population. Other signs that may present are iris whorling (distorted radially orientated iris), ‘glaucomfleken’, lens opacities, and excessive

pigmented trabecular meshwork. Significant optic nerve damage is absent. Patient can be asymptomatic or symptomatic (Foster *et al.*, 2002; Aung, 2005).

3.7.2.1 Acute Primary Angle Closure (Acute PAC)

Acute PAC is symptomatic PAC in which acute episode of angle closure occurs. This attack may happen at any stage during the disease but leaves no detectable nerve damage following prompt treatment (Foster *et al.*, 2002; Aung, 2005).

3.7.3 Primary Angle Closure Glaucoma (PACG)

PACG is the final sequelae of the event. There is evidence of glaucomatous optic neuropathy with or without visual field loss, in combination with changes seen in PAC (Foster *et al.*, 2002; Aung, 2005).

3.7.4 Peripheral Anterior Synechiae (PAS)

PAS is detectable on gonioscopy. It refers to adhesion of peripheral iris to the anterior angle structures, most commonly the functional trabecular meshwork. Rarely it may extend to the Schwalbe's line. Characteristically, PAS are broad and irregular adhesions, bridge the angle recess, obscure the underlying structures, inhibit posterior movement of iris on indentation, and drag normal iris vessels with it (Nema & Nema, 2014).

3.7.5 Intraocular Pressure (IOP)

IOP is defined as tension inside the eyeball. It is measured with tonometer, either through contact or non-contact method. Bilateral IOP can be symmetric or asymmetric. IOP does fluctuate, throughout the day (short term) or over longer intervals (long term). Normal IOP range is between 10 to 21 mmHg (Alimuddin, 1956). IOP above 21 mmHg is abnormal. IOP is the only modifiable risk factor affecting glaucoma progression (Coleman *et al.*, 2004; Bengtsson *et al.*, 2007; Caprioli & Coleman, 2008; Anderson, 2003).

3.7.5.1 Mean IOP

Mean IOP is defined as average of IOP readings at particular point of time or period (Liu *et al.*, 1999). Mean IOP at 4-hourly interval and overall mean peak IOP during 24-hour period has been described in details of methodology (refer 3.9.2.2).

3.7.5.2 Mean Peak IOP

Peak IOP is defined as maximum IOP reading during 24-hour period (Baskaran *et al.*, 2009). Mean peak IOP at 4-hourly interval and overall mean peak IOP during 24-hour period has been described in details of methodology (3.9.2.3).

3.7.5.3 Mean Trough IOP

Trough IOP is defined as minimum IOP reading during 24-hour period (Baskaran *et al.*, 2009). Mean peak IOP at 4-hourly interval and overall mean peak IOP during 24-hour period has been described in details of methodology (refer 3.9.2.4).

3.7.5.4 Mean IOP Fluctuation

Overall mean IOP fluctuation is defined as the difference between the peak IOP and the trough IOP during 24-hour period (Baskaran *et al.*, 2009). In this study, Mean IOP fluctuation at 4-hourly interval is defined as the difference between IOP values at each interval. IOP at each interval was calculated by subtracting lower IOP value from higher IOP value.

Mean IOP fluctuation at 4-hourly interval and overall mean IOP fluctuation during 24-hour period has been described in details of methodology (refer 3.9.2.5).

3.7.6 Circadian Rhythm of IOP

Circadian rhythm of IOP is defined as daily rhythmic activity cycle based on 24-hour period. It consists of peaks and troughs at different period of daytime (diurnal) and nighttime (nocturnal).

Each eye's circadian rhythm was classified as having one of the following 3 patterns of peak; morning, afternoon and night; and 3 patterns of trough; morning, afternoon, and night (Sihota *et al.*, 2005).

3.7.6.1 Peak Pattern

Peak pattern is defined as the maximum mean IOP readings at particular period of morning, afternoon, or night (Sihota *et al.*, 2005). Measurement of peak pattern has been described in details of methodology (refer 3.9.2.6).

3.7.6.2 Trough Pattern

Trough pattern is defined as the minimum mean IOP readings at particular period of morning, afternoon, or night (Sihota *et al.*, 2005). Measurement of trough pattern has been described in details of methodology (refer 3.9.2.6).

3.7.7 Visual Field

3.7.7.1 AGIS VF Score

This is an objective, quantitative method of scoring test reliability and severity of glaucomatous field loss using Humphrey Visual Field Analyzer. It was initially developed and used for Advanced Glaucoma Intervention Study (AGIS 2, 1994). Method of Humphrey VF assessment and AGIS score has been described in details of methodology (refer 3.9.3.1 and 3.9.3.2).

3.7.7.2 Progression of VF Loss

3.7.7.2.1 Progressed eye group of PACG

It is defined as the first occurrence in an eye, at 3 consecutive 6-monthly visits, of worsening in the VF score of ≥ 4 from the baseline value; changes in the AGIS VF defect score are measured from pre-intervention reference values (AGIS 2, 1994).

3.7.7.2.2 Non-progressed eye group of PACG

It is defined as VF score of ≤ 3 from the baseline value (AGIS 2, 1994).

3.8 Study Instruments

3.8.1 Slit Lamp Biomicroscopy

The Topcon slit lamp, model Topcon SL-3F (Topcon, Japan) was used for slit lamp examinations.

3.8.2 Goldmann Applanation Tonometer

The Haag-Streit Goldmann applanation tonometer was also used to take IOP measurements. It was calibrated monthly with a standard tonometer calibrator.

3.8.3 Goldmann Three Mirror Lens

The Goldmann three mirror lens was used to assess the anterior chamber angles. Angles then were graded based on Shaffer classification.

3.8.4 Humphrey Visual Field Analyzer

The Humphrey Visual Field Analyzer II model 750i was used for subjective assessment of patient's visual field. It is a type of static, automated, computerized perimetry. Incorporated program used was Swedish Interactive Threshold Algorithm Standard (SITA-Standard) strategy with 24-2 test pattern.

3.8.5 Eye Drops

i. Guttae Proparacaine Hydrochloride 0.5% (Alcaine)

This is topical anaesthesia of rapid and short-acting type. It is preserved with benzalkonium chloride 0.01%. It was used to anaesthesized cornea in facilitating Goldmann applanation tonometry procedure and gonioscopy.

ii. Guttae Tropicamide 1% (Mydriacyl)

This is a topical muscarinic antagonist of short-acting type. It was used to dilate pupils for fundus examination specifically optic disc clinical assessment.

3.8.6 Fluorescein Sodium Strip

Fluorescein sodium strip (Fluorets, Chauvin) was used with guttae proparacaine hydrochloride 0.5% to stain cornea to facilitate IOP measurement with Goldmann applanation tonometer.

3.8.7 90 Diopter Lens

The 90D (Volk, Germany) non-contact lens was used with slit lamp for fundus viewing to assess optic nerve head.

Figure 3.1: Humphrey Visual Field Analyzer model 750i

Figure 3.2: Goldmann Applanation Tonometer mounted on slit lamp

Figure 3.3: Gutt proparacaine 0.5%

Figure 3.4: Fluorescein sodium strip

3.9 Details Of Methodology

3.9.1 Recruitment of Study Group

Recruitment of study cases consisted of patients with established diagnosis of PACG and attending regular visits in Ophthalmology Clinic, Hospital Universiti Sains Malaysia. Basic slit lamp examination and visual acuity assessment with Snellen chart was performed prior to enrollment. Patients were screened for inclusion and exclusion criteria, only those eyes that met the inclusion criteria were selected. Due to the small number of patients and that each eye may behave differently thus having differing rates of progression, both eyes were included from the same subject. There were 50 eyes from 25 patients enrolled in the study. Nature and detail of the study were explained to patients. Informed consent was obtained from patients who agreed to participate in this study.

Demographic data was documented. A detailed history was acquired from the patients regarding age, sex, race, history of systemic diseases, duration of follow-up, history of acute PAC, past cataract surgery, and number and type of IOP lowering agents used.

Patients underwent 2 times of examination, as outpatient in clinic and as inpatient in ward. In clinic, complete ophthalmologic examination, which comprised of slit lamp examination, baseline IOP measurement, funduscopy, and gonioscopy. Reliability of latest documented HVF test and the previous documented HVF of at least 6 months apart were checked. If the test was not reliable, it was repeated and only reliable

result was taken. For each eye, AGIS score was calculated from the HVF results. Each eye then was grouped into progressed or non-progressed group, based on AGIS score of visual field glaucoma progression. Patients subsequently were given date for one day ward admission.

During admission in the ward, patients' vital signs were documented. All oral or topical medications including IOP lowering agents were continued. There were 6 readings of timely IOP measurements. IOP measurements were performed using GAT every 4 hours over 24-hour period; at 0800 hour (8 am), 1200 hour (12 pm), 1600 hour (4 pm), 2000 hour (8 pm), 2400 hour (12 am), and 0400 hour (4 am). IOP was measured within 30 minutes after the each point of interval time. All data were recorded in the data collection form. Patients were discharged from ward next morning, upon completion of latest IOP measurement at 4 am.

3.9.2 Methods of IOP Measurement

3.9.2.1 Goldmann Applanation Tonometer

This procedure was preceded by instillation with a topical anesthetic drop and followed by fluorescein dye. The patient was seated at the slit lamp with his/her forehead firmly against the headrest and chin comfortably on the chin rest. Patient was instructed to look straight ahead and to open eyelids widely. Patient was then instructed to blink once to spread the fluorescein dye. Adequate fluorescent staining is essential for accurate tonometry. He/She was advised not to blink, squeezing or

holding his/her breath. Biprism of tonometer head was moved gently forward until just touched the cornea. Knob was slowly and gently adjusted to obtain IOP.

3.9.2.2 Measurement of Mean IOP and Overall Mean IOP

Mean IOP at 4-hourly interval were values of IOP that were averaged at each time point were averaged to each group. There were 6 mean IOP for 6 measurements for each group.

In this study, for overall mean IOP during 24-hour period, values of mean IOP from 6 measurements (at 4-hourly interval) were averaged for each group.

3.9.2.3 Measurement of Mean Peak IOP and Overall Mean Peak IOP

In this study, a single of peak IOP from the 6 measurements was obtained from each eye. If one eye had maximum IOP reading at more than 1 interval, the first interval of peak IOP reading was taken according to chronological 4-hourly interval. There may be none of eyes that had peak IOP reading at a particular interval.

For mean peak IOP at 4-hourly interval, values of peak IOP at each interval were averaged for each group. There were 6 mean peaks IOP for 6 measurements for each group.

For overall mean peak IOP during 24-hour period, values of mean peak IOP from 6 measurements (at 4-hourly interval) were averaged for each group.

3.9.2.4 Measurement of Mean Trough IOP and Overall Mean Trough IOP

In this study, a single of trough IOP from the 6 measurements was obtained from each eye. If one eye had minimum IOP reading at more than 1 interval, the first interval of trough IOP reading was taken according to chronological 4-hourly interval. There may be none of eyes that had trough IOP reading at a particular interval.

For mean trough IOP at 4-hourly interval, values of trough IOP at each interval were averaged for each group. There were 6 mean troughs IOP for 6 measurements for each group.

For overall mean trough IOP during 24-hour period, values of mean trough IOP from 6 times measurement (at 4-hourly interval) were averaged for each group.

3.9.2.5 Measurement of Mean IOP Fluctuation and Overall Mean IOP Fluctuation

Mean IOP fluctuation at 4-hourly interval is defined as the difference between IOP values at each interval. IOP at each interval was calculated by subtracting lower IOP value from higher IOP value.

For example, IOP fluctuation at 0800 hour was calculated by subtracting IOP value at 1200 hour from IOP value at 0800 hour (whichever lower value, was subtracted from the higher value).

There were 6 IOP fluctuations for 6 measurements for each group.

For overall IOP fluctuation during 24-hour period, values of IOP fluctuations from 6 measurements (at 4-hourly interval) were averaged for each group.

3.9.2.6 Measurement of Peak Pattern in Circadian Rhythm of IOP

In this study, a single of IOP trough from the 6 measurements of IOP at 4-hourly interval was obtained from each eye (refer 3.7.5.2). The point of time that the peak pattern occurred was documented. The eye was classified as ‘morning’ peak, if the peak was recorded at 0400 or 0800 hour, ‘afternoon’ peak, if recorded at 1200 or 1600 hour, and ‘night’ peak, if recorded at 2000 or 2400 hour.

3.9.2.7 Measurement of Trough Pattern in Circadian Rhythm of IOP

In this study, a single of IOP trough from the 6 measurements of IOP at 4-hourly interval was obtained from each eye (refer 3.7.5.3). The point of time that the trough occurred was documented. The eye was classified as ‘morning’ trough, if the trough was recorded at 0400 or 0800 hour, ‘afternoon’ trough, if recorded at 1200 or 1600 hour, and ‘night’ trough, if recorded at 2000 or 2400 hour.

3.9.3 Method of Visual Field Assessment

3.9.3.1 Humphrey Visual Field (HVF) Test

HVF was carried out monocularly. SITA Standard 24-2 program was applied. Standard stimulus size III ($4mm^2$) was chosen. Prior to the procedure, patient’s refractive error and presbyopia was corrected using appropriate glasses or lens on trial frame. Care was taken to center the patient close to correcting lens to avoid a lens rim artifact. Pupils were not dilated. Patient was instructed to maintain fixation

at central target (yellow light) throughout the procedure, while peripheral vision being tested.

3.9.3.2 AGIS score

Patient was further stratified according to severity of the disease using Modified AGIS scoring with reliable Humphrey Visual Field (HVF) 24-2 or 30-2 using Humphrey Field Analyzer 750i (AGIS 2, 1994). The latest HVF of at least 3 month from current visit was used in this study. Reliable HVF was the visual field that was reproducible on 2 consecutive visual field analyses. If there was no reliable or latest HVF, another HVF was done and considered as latest HVF. This score was obtained from the total deviation plot of HVF 24-2 or 30-2. Reliability of visual field was based on percentage of fixation loses (less than 20%), false-positive response (less than 33%) and false-negative response (less than 33%) (AGIS 2, 1994). The unreliable visual field was repeated on the next visit, within 2 to 4 weeks apart. However, if after 3 attempts it was still unreliable, the patient was excluded from the study and given appointment date as in regular follow up in eye clinic.

A point was considered defective when a minimum amount of sensitivity depression was reached. A special transparent plastic was designed according to AGIS score and was placed on subject or patient's HVF. The AGIS score was conducted by Dr Haslinda (primary investigator) and masked glaucoma consultant Professor Dr Liza Sharmini Ahmad Tajudin re-scored the HVF.

The classification of severity was based on mean AGIS score (AGIS 2, 1994). Score for each hemifield and for nasal area were summed. The maximum possible score was 20 (two for nasal field and nine for each hemifield). Severity was divided into five stages. 0 as normal, 1-5 for mild, 6-11 for moderate, 12-17 for severe, 18-20 for end stage of glaucoma.

3.10 Statistical Analysis

Statistical analysis was performed with the “Statistical Package for Social Sciences” (SPSS) for Macintosh version 22 software.

Data exploration and cleaning was done before analysis. Descriptive statistic numerical data was checked for normality distribution. Normally distributed data was reported using mean and standard deviation, while non-normal or skewed data was reported using median and interquartile range.

Univariate analysis was done for comparison of baseline. For numerical data with normative value, independent t test was used to compare the means between 2 independent samples. For skewed distribution data, Mann-Whitney U test was used for numerical variable; where as Fisher’s exact test was used for categorical variable. In each of the statistical analysis, p value of <0.05 was deemed as statistically significant.

3.11 Plans Of Minimizing Error

These were the steps used to minimize the errors while conducting the study:

1. Subjects were selected according to the inclusion and exclusion criteria.

2. The same instruments and equipments were used for measurement in the study.

3. The AGIS score was conducted by single primary investigator (Dr Haslinda A. Rahim @ Samsuddin) and masked single glaucoma consultant Professor Dr Liza Sharmini Ahmad Tajudin re-scored the HVF.

4. The principal investigator (Dr Haslinda A. Rahim @ Samsuddin) was the single operator in the measurement of the intraocular pressure.

CHAPTER 4
RESULTS

4.1 Demographic Data

4.1.1 General Demographic Data

A total of 50 eyes from 25 PACG patients were included in the study. They were grouped into eyes that were progressed and eyes that were non-progressed. The progressed PACG consist of 11 eyes, while non-progressed PACG consist of 39 eyes.

Out of 25 PACG patients, 7 patients had bilateral non-progressed eyes, 2 patients had bilateral progressed eyes, and 16 patients had progressed and non-progressed eyes.

In general, patients who had bilateral progressed eyes were older. There was female preponderance among PACG patients. Malays outnumbered Chinese patients. Hypertension was the commonest systemic co-morbidity.

Table 4.1: Demographic data of PACG patients

Characteristics	PACG patients N= 25
Age (mean,SD)	64 (9.4)
Sex (n,%)	
Male	10 (40.0)
Female	15 (60.0)
Race (n,%)	
Malay	19 (76.0)
Chinese	6 (24.0)
Systemic disease (n,%)	
Hypertension	
• Yes	15 (60.0)
• No	10 (40.0)
Diabetes mellitus	
• Yes	9 (36.0)
• No	16(64.0)
Hyperlipidemia	
• Yes	10 (40.0)
• No	15(60.0)
Laterality, (n,%)	
• Unilateral progressed & non-progressed	16 (64.0)
• Bilateral progressed	2 (8.0)
• Bilateral non-progressed	7 (28.0)

4.1.2 Clinical Characteristics

The median intraocular pressure at presentation was slightly higher in progressed PACG but this was not statistically significant. There was significant difference for duration of diagnosis. Progressed PACG was being followed up longer from initial presentation as compared to non-progressed PACG.

There was significant difference for AGIS score at initial diagnosis and at requirement.

Peripheral iridectomy was patent in all eyes. There was no significant difference in the presence of previous acute primary angle closure, pseudophakia, and central corneal thickness (Table 4.2).

All progressed PACG were on either triple or quadruple topical pressure lowering agents, which was statistically significant as compared to non-progressed PACG. The types of present topical pressure lowering agents also showed significant difference (Table 4.3).

Table 4.2: Comparison of clinical characteristics data between progressed and non-progressed PACG

Characteristics	Eyes with PACG N=50		p-value
	Progressed n=11	Non-progressed n=39	
Duration of diagnosis, years median (IQR)	6.0 (6.0)	2.0 (2.0)	**<0.001**[#]
Intraocular pressure at presentation, mmHg median (IQR)	23.0 (14.0)	22.0 (8.0)	0.255[#]
History of previous acute Primary Angle Closure (n,%)	4 (36.4)	5 (12.8)	0.093*
Central corneal thickness, mm (mean, SD)	522 (0.2)	513 (0.2)	0.162[@]
AGIS score at initial diagnosis (n,%)			**0.001***
None	1 (9.1)	0 (0)	
Mild	2 (18.2)	29 (74.4)	
Moderate	8 (72.7)	9 (23.1)	
Severe	0 (0)	1 (2.6)	
AGIS score at recruitment (n,%)			**<0.001***
Mild	0 (0)	29 (74.4)	
Moderate	2 (18.2)	9 (23.1)	
Severe	9 (81.8)	1 (2.6)	
Laser peripheral iridectomy (n,%)	11 (100)	39 (100)	-
Pseudophakia (n,%)	5 (45.5)	11 (28.2)	0.233*

$p<0.05$ is considered statistically significant based on [@]independent t-test, [#]Mann-Whitney U test, *Fisher's exact test

Table 4.3: Comparison of number and types of topical pressure lowering agents between progressed and non-progressed PACG

Characteristics	Eyes with PACG N=50		p-value
	Progressed n=11	Non-progressed n=39	
Number of present topical pressure lowering agents (n,%)			**<0.001***
None	0 (0)	4 (10.3)	
Monotherapy	0 (0)	17 (43.6)	
Dual therapy	0 (0)	10 (25.6)	
Triple therapy	6 (54.5)	4 (10.3)	
Quadruple therapy	5 (45.5)	4 (10.3)	
Types of present topical pressure lowering agents (n,%)			**0.001***
No drug	0 (0)	4 (10.3)	
BB alone	0 (0)	14 (35.9)	
PG alone	0 (0)	2 (5.1)	
CAI alone	0 (0)	1 (2.6)	
BB + PG	0 (0)	3 (7.7)	
BB + CAI	0 (0)	7 (17.9)	
BB + PG + CAI	6 (54.5)	4 (10.3)	
BB + PG + CAI + AB	5 (45.5)	4 (10.3)	

$p<0.05$ is considered statistically significant based on *Fisher's exact test

BB = Beta Blocker, PG = Prostaglandin analogue, CAI = Carbonic Anhydrase Inhibiter, AB = Alpha Blocker

4.2 Pattern of 4-hour Time Points of IOP Variables in Progressed and Non-progressed PACG

In progressed PACG, both mean IOP and IOP peak were at maximum reading at 0800 hour. Mean IOP were noted at minimum reading at 1200 hour while IOP trough was at minimum reading at 2400 hour.

No progressed eyes had IOP peak at 1200 hour or had IOP trough at 0400 hour. Maximum IOP fluctuation occurred at 1200 hour and minimum IOP fluctuation occurred at 0400 hour.

Meanwhile, in non-progressed PACG, maximum mean IOP was observed at 0800 hour with IOP peak of maximum reading at 2400 hour. Minimum mean IOP was observed at 2000 hour with minimum IOP trough occurred at 0800 hour. Maximum IOP fluctuation occurred at 2400 hour and minimum IOP fluctuation occurred at 0400 hour.

Generally, mean IOP at 4-hour time points were almost similar between progressed and non-progressed PACG from 1600 to 2400 hour. Largest difference was observed between groups at 1200 hour. Mean IOP of non-progressed PACG decreased steadily from 0800 to 2000 hour, and increased steadily after that.

Progressed PACG showed consistently lower mean IOP fluctuation from non-progressed eye group between 0800 and 2000 hour. There was a single interval where mean IOP of progressed PACG was higher than non-progressed PACG, which occurred at 2400 hour, but the difference was small.

At 4-hour time points, there were consistent IOP peak readings in non-progressed PACG as compared to progressed PACG. Both groups exhibited large difference of IOP peak reading at 2400 and 0400.

There were 2 time points of IOP trough where progressed PACG had higher reading than non-progressed PACG, which occurred at 0800 and 1600 hour. Progressed PACG exhibited plateau reading of IOP trough between 1200 and 1600 hour, and 2000 and 2400 hour. IOP trough reading of non-progressed PACG decreased steadily from 2000 to 0400 hour.

IOP fluctuation reading at 4-hour time points in progressed PACG decreased steadily from 1200 to 0400 hour but it showed consistently higher reading than non-progressed PACG between 1200 and 2000 hour. Non-progressed PACG had higher IOP fluctuation reading than progressed PACG at 2400 to 0400 hour. Both groups had overlapping IOP fluctuation reading at 0800 hour. Mean IOP fluctuation at 4-hour time points ranged between 1.6 to 3.0 mmHg in progressed PACG, and it ranged 2.0 to 2.9 mmHg in non-progressed PACG.

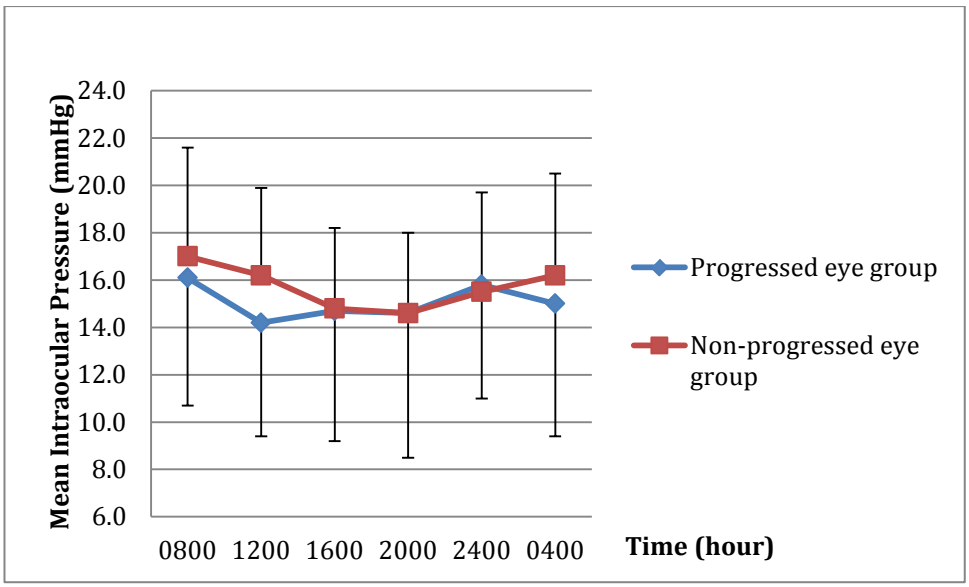

Figure 4.1 Mean IOP in progressed and non-progressed PACG at 4-hour time points

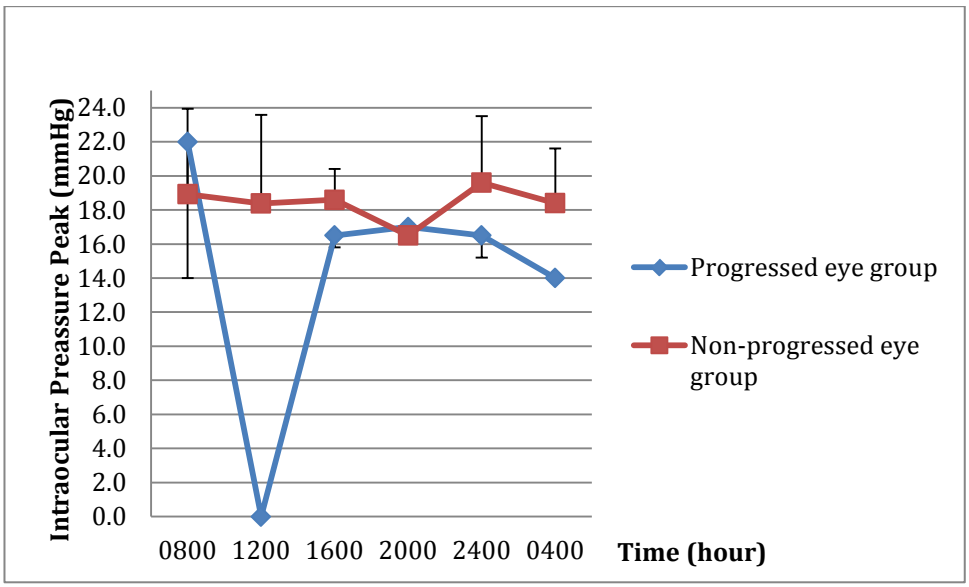

Figure 4.2 Mean of IOP peak in progressed and non-progressed PACG at 4-hour time points

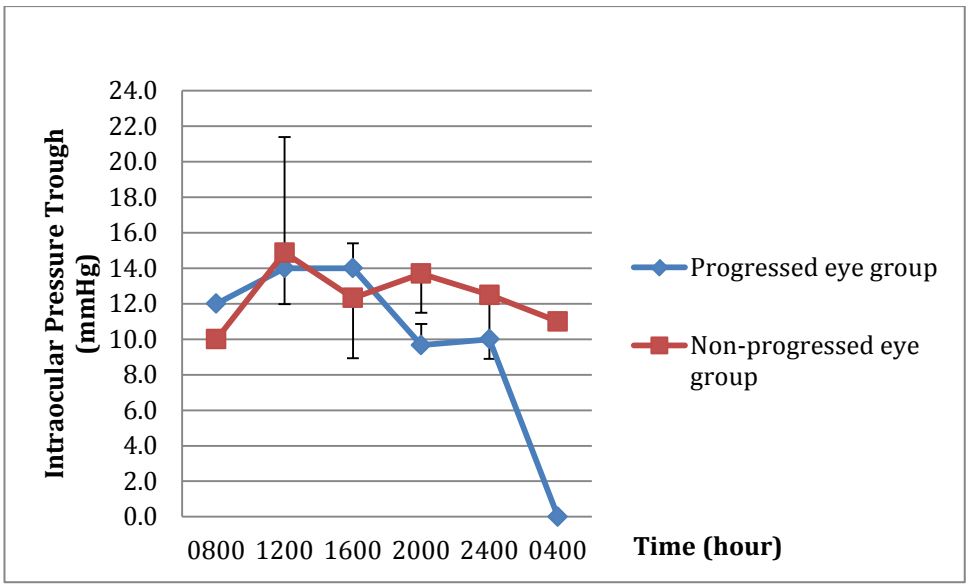

Figure 4.3 Mean of IOP trough in progressed and non-progressed PACG at 4-hour time points

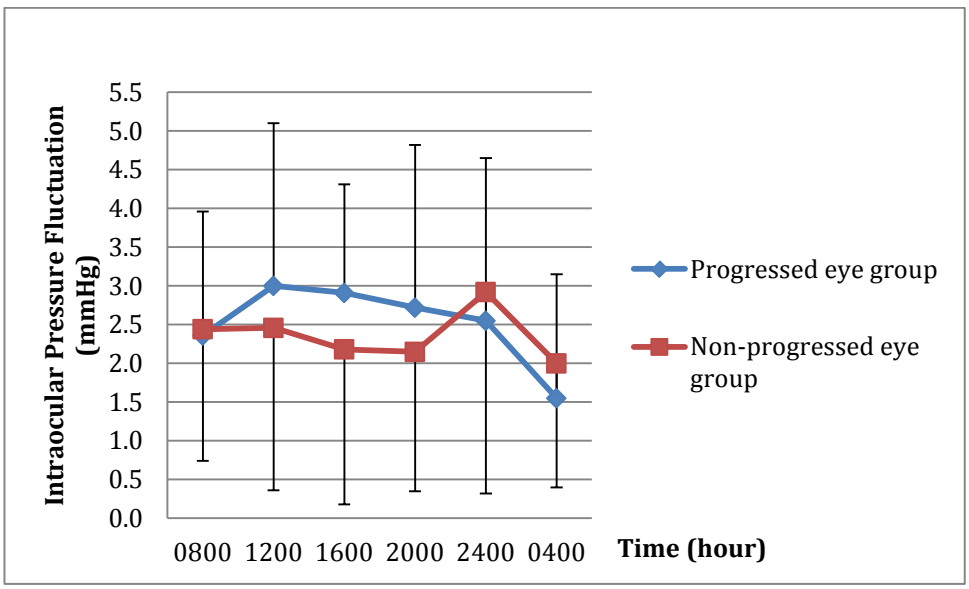

Figure 4.4 Mean of IOP fluctuation in progressed and non-progressed PACG at 4-hour time points

4.3 Pattern of Circadian Rhythm of IOP in Progressed and Non-progressed PACG

Majority of progressed PACG showed patterns of night peak with afternoon trough, while non-progressed PACG exhibited patterns of afternoon peak with night trough. This is however not statistically significant.

Table 4.4: Comparison of peak and trough pattern between progressed and non-progressed PACG

Characteristics	Eyes with PACG N=50		p-value*
	Progressed n=11	Non-progressed n=39	
Peak (n,%)			0.130
Morning	4 (16.7)	20 (83.3)	
Afternoon	2 (13.3)	13 (86.7)	
Night	5 (45.5)	6 (54.5)	
Trough (n,%)			0.881
Morning	1 (20)	4 (80)	
Afternoon	6 (26)	17 (73.9)	
Night	4 (18.2)	18 (81.8)	

$p<0.05$ is considered statistically significant based on *Fisher's exact test

4.4 Comparison of 24-hour Intraocular Pressure Variables between Progressed and Non-progressed PACG

There was no significance difference for 24-hour mean IOP, IOP peak, IOP trough, and IOP fluctuation between progressed and non-progressed PACG.

Table 4.5: Comparison of 24-hour mean IOP, IOP peak, IOP trough, and IOP fluctuation between progressed and non-progressed PACG

Characteristics	Eyes with PACG N=50		p-value[#]
	Progressed n=11	Non-progressed n=39	
24-hour IOP, mmHg (median, IQR)	13.7 (3.2)	15.3 (5.5)	0.202
24-hour IOP peak, mmHg (median, IQR)	17.0 (3.0)	18.0 (5.0)	0.285
24-hour IOP trough, mmHg (median, IQR)	11.0 (4.0)	13.0 (4.0)	0.151
24-hour IOP fluctuation, mmHg (median, IQR)	6.0 (3.0)	6.0 (3.0)	0.803

IQR = Interquartile Range

$p<0.05$ is considered statistically significant based on [#]Mann-Whitney U test

CHAPTER 5
DISCUSSION

5.1 Discussion

Visual field progression among PACG patients was less extensively studied as compared to glaucoma progression of angle closure between subtypes from PACS to PAC, and PAC to PACG. It was well known that the natural course of PACG begins with PACS, which may worsen to become PAC and further developed into PACG (Aung, 2005). Once glaucomatous damage has occurred, there was 16-fold increased risk of progression in Malays PACG patients (Liza-Sharmini *et al.*, 2014).

IOP is among important risk factors contributing to glaucoma progression, apart from other factors such as thinner CCT, short axial length, glaucomatous changes at presentation, advanced VF defect at presentation, presence of APAC, absence of laser PI, older age, Malay ethnic, lower blood pressure, and presence of migraine (Hong *et al*, 2007; Fan *et al*, 2013; Liza-Sharmini *et al*, 2014; Quek *et al*, 2011; Leske *et al*, 2004; Sharmini *et al*, 2009; Drance et al, 2001).

High IOP alone was insufficient to explain the progression of glaucomatous optic neuropathy in patients with 'normal' IOP during clinic visits. More studies are looking into wide diurnal IOP fluctuation in addition to high mean IOP as significant risk for glaucoma progression (Asrani et al., 2000; Nouri-Mahdavi et al., 2004; Singh & Shrivastava, 2009). Diurnal and nocturnal IOP recordings are difficult and pose a practical challenge for both clinician and patients. Many studies required hospital admission for nocturnal IOP recordings. It has to be borne in mind that the effort of recording IOP during sleep itself can be a confounding factor (Weinreb & Liu, 2006).

In general, the progression rate of PACG was related to higher average of highest IOP in each year of follow up (Lee *et al.*, 2004). Currently, high mean IOP and wide IOP fluctuation was consistently demonstrated as important predictors of glaucoma progression. However, majority of the studies were conducted on POAG rather than PACG subjects (Coleman *et al.*, 2004; Bengtsson *et al.*, 2007; Caprioli & Coleman, 2008; Anderson, 2003; Asrani *et a.l*, 2000).

The progressed and non-progressed PACG in this study were determined based on AGIS score from Humphrey visual field test. AGIS scoring system was chosen as it has greater reproducibility, good specificity, and high sustainability (Katz, 1999; Heijl *et al*, 2008). AGIS system is an event-based progression analysis, that determines VF progression to be either present or absent depending on a predefined change in the VF parameters (Rao *et al*, 2013). However, AGIS system was seldom used in glaucoma studies nowadays as it was very conservative. Trend-based progression analysis such as VF index, was preferred as it provides the actual rate of change in the VF parameters (Rao *et al*, 2013). From this analysis, the rate of progression (ROP) can also be determined so that the treatment can be more aggressive in fast progressers. In our clinic setting, we have limitations of using VFI for regular monitoring of glaucoma progression due to inadequate facilities to accommodate high number of glaucoma patients turnover.

Sample size calculation in our study was based on Baskaran's work (Baskaran et al, 2009). Standard deviation of mean IOP of 1.24 mmHg was used. However for better accuracy, standard deviation of IOP fluctuation should be considered instead of mean IOP alone. Since the standard deviation of mean IOP fluctuation was 2.4 mmHg

(Baskaran et al, 2009) as compared to mean IOP of 1.24 mmHg (Baskaran et al, 2009), it is expected the sample size to be increased by minimum of 3-folds which render longer duration of study period.

A total of 50 eyes from 25 PACG patients were included in the study. They were grouped into eyes that were progressed and eyes that were non-progressed. The progressed eye group consist of 11 eyes, while non-progressed eye group consist of 39 eyes. We had included bilateral eyes of patients diagnosed with PACG, where one eye may be grouped in progressed PACG and the fellow eye may be grouped in non-progressed PACG. Both eyes also may be grouped into one similar group. Majority of our patients had non-progressed eyes bilaterally. Non-progressed eye group had larger sample size than the progressed group. There is possibility of symmetry of right versus left IOP over 24 hours in a patient's eyes, as proposed by Sit and colleagues. They observed that there was moderate strength of association between IOPs of right and left eyes in untreated glaucoma patients (Sit *et al*, 2005). This condition may apply to a patient's eyes that were grouped into different groups of progressed and non-progressed PACG.

We had included pseudophakic patients in our study. As widely known, the crystalline lens is a major contributor of angle closure in PACG patients. Cataract extraction has been found to indirectly relieve pupillary block and lower IOP in angle closure glaucoma. It helps to widen the narrow angle, deepen the anterior chamber, and attenuate the anterior positioning of ciliary processes (Aung *et el.*, 2001). But once the lens is removed, the widening of anterior chamber angle can blur the distinction between open-angle and angle-closure glaucoma.

Thus in future study, it is recommended that pseudophakia is one of exclusion criteria.

As in nature course of any chronic disease; the longer the duration of the disease there is the higher risk to progress. Length of follow up also has been found to be a risk factor for glaucoma progression (Nouri-Mahdavi *et al.*, 2004). Progressed eye PACG in this study were being followed up longer at average 6 years as compared to non-progressed eye group of PACG at average 2 years, which was statistically significant. The differences in follow-up duration between the groups substantively may weaken the comparisons of the 24-hour IOP profiles. Thus, comparable of follow-up period between groups will definitely provide more valuable data.

There was also significant difference in number and types of pressure lowering agents in both groups. All progressed eyes were on more than 3 topical pressure lowering agents as compared to non-progressed eyes whom majority were on less than 2 medications. The 24-hour IOP profile would have corresponded to the effect of IOP lowering medications, not the angle closure alone. Hence the washout period may overcome the medication effect. However in this study we opted to continue with patients' current medications as the PACG eyes were at risk for acute attack and fast deterioration of neuropathy especially those eyes with severe stage of disease.

From this study, we observed almost similar pattern of some IOP variations at 4-hour time points between progressed and non-progressed PACG. In both groups, highest mean IOP was recorded in the morning, which was at 0800 hour with maximum IOP peak reading. While lowest mean IOP was recorded at noon in progressed eyes, non-

progressed eyes exhibited lowest mean IOP at night. Majority of progressed PACG showed patterns of night peak with afternoon trough, while non-progressed PACG exhibited patterns of morning peak with night trough. This result was in agreement with other studies, which reported that IOP peak in PACG subjects was observed at various time in the morning, afternoon, early morning, and also midnight (Sihota *et al.*, 2005; Leydhecker, 1976; Shapiro & Zauberman, 1979).

Over 24-hour period, non-progressed PACG exhibited slightly higher reading of mean IOP, IOP peak, and IOP trough than progressed PACG even though it was not statistically significant. Mean IOP was significantly higher in progressed than non-progressed PACG and significantly associated with PACG progression, as showed in other 2 studies (Sharmini *et al*, 2009; Quek *et al*, 2011). Sharmini and workers also recommended that mean IOP target should be equal or less than 12 mmHg as they observed none of their PACG patients progressed with the IOP reading, while more than half of the patients progressed with IOP of equal or more than 22 mmHg. On the other hand, Quek and friends documented 33% of their treated PACG patients progressed over 10 years, and 5 to 10% progressed to blindness over similar period. Again, these 2 studies differ from our study in terms of setting and duration of IOP measurements.

A study by Lee and colleagues, which compared rate of VF progression between PACG and POAG, demonstrated that VF progression was faster in PACG. In PACG, progression of VF loss was significantly correlated with mean IOP, IOP peak, and IOP trough (Lee *et al*, 2004). Konstas and associates conducted a study in POAG and they concluded that 24-hour IOP peak is an independent risk factor for POAG

progression (Konstas *et al*, 2012). Both also differ from our study as they compared either PACG and POAG, or progressed and non-progressed POAG.

There are various definitions for IOP fluctuation. In our study, we defined IOP fluctuation as difference between IOP measurements at each time points by subtracting lower IOP value from higher IOP value. The 24-hour IOP fluctuations were the mean of IOP fluctuations from all time points. Other definition of IOP fluctuation is the standard deviation of IOP measurements (Baskaran *et al*, 2009; Rao *et al*, 2013). We used this definition for our study because the IOP was measured 4-hourly around the clock. Different setting of methodology of IOP fluctuation measurements in other studies were conducted, for example Baskaran's work employed only diurnal period. On the other hand, Rao's study was conducted over more than 5 years follow up with different time of single office hour IOP measurement at 3 to 6-monthly interval.

In our study, IOP fluctuation over 24-hour recordings was 6.0 mmHg in both groups. High diurnal IOP fluctuation of within range of 4-8 mmHg has been observed in PACG eyes (Baskaran *et al.*, 2009; Sihota *et al*, 2005). Our finding was in agreement with both studies. However, there was no significant difference between progressed and non-progressed PACG for 24-hour IOP fluctuation. This was an unexpected result, considering that greater IOP dependence for optic nerve damage was observed in PACG (Gazzard *et al*, 2003). Small sample size, bilateral eyes inclusion, and different duration of follow-up may contribute to this insignificance result.

Rao and colleagues had investigated relationship between IOP and rate of VF progression in treated PACG. They found out that IOP fluctuation was significantly associated with PACG progression. Each 1 mmHg increase in IOP fluctuation will worsen the progression by 0.35% per year (Rao *et al*, 2013). Another work by Hong and associates pointed that larger long term IOP fluctuation was associated with PACG progression even though IOP maintained low post triple procedure (Hong *et al*, 2007). These 2 studies concluded the significance of IOP fluctuation as risk factor for PACG progression, but none are comparable to our study. Both studies took 5 to 10 years of follow-up, and single office visit mean IOP was taken. Our studies recorded a one-day IOP profile, which was 24-hour IOP measurement of 6 time points. Hence our study were subjected to short-term IOP fluctuations, where as their studies were prone to long-term IOP fluctuations. Furthermore, one of the studies recruited post triple procedure patients where as our study excluded patients post filtering surgery.

Regarding circadian rhythm of IOP, normal non-glaucoma people were observed to have morning and night peak, while the trough occurs in the afternoon. This normal circadian rhythm is explained by the physiology of aqueous production and outflow as well as the change in body position (Grehn and Stamper, 2009). Aqueous production is maximized during daytime with morning peak, thus giving rise to IOP peak at that point of time. To add on, multiple 'stressful' activities in the morning to start the day with such as quick preparing and sending children to school, rushing to workplace, and settling last minute errands also indirectly might justify the IOP peak in the morning. During daytime, the body is mostly in sitting or upright position. The effect of gravity in that position contributes to the trough that occurs in the afternoon,

facilitating aqueous humor outflow despite its maximum production. The body is also in more relaxed condition in the afternoon after settling the ‘stressful’ morning activities. At night, while aqueous production decreased by 50% or more, there is also reduction in outflow facility as the body changes its position from seated to supine, in which causes episcleral venous pressure to raise. This results in peak of IOP at nighttime.

In glaucoma patients, the circadian rhythm of IOP has been known to be interrupted and dysfunction (Jean-Louis *et al.*, 2008; Fogagnolo *et al.*, 2009). Progressed PACG demonstrated night peak while non-progressed PACG exhibited morning peak. For trough, progressed PACG showed afternoon trough while non-progressed PACG showed night trough.

In our study, we found that the progressed eye group of PACG followed the normal circadian control of IOP, but this was not the case with the non-progressed eye group. This could be explained by significant difference of pharmacotherapy between both groups. Majority of progressed eyes received prostaglandin analogue in their treatment. Prostaglandin analogue has been claimed to maintain a significant IOP reduction around-the-clock hence plays an important role in circadian IOP management (Mishima *et al.*, 1997). It helps to increase uveoscleral outflow especially nighttime where the aqueous humor outflow facility is at minimum level.

Apart from that, there are factors affecting IOP fluctuation measurement that should be addressed. In this study, we admitted our patients to hospital ward for 24 hours. As GAT was used as IOP measurement, patients had to be awake during

examination. Patients also had to walk from bed, entered examination room, and properly seated for IOP measurement. Some of the patients were unable to sleep overnight probably because of sudden change in environment. Sleep also was disturbed by frequent repeated IOP measurements. Their activity daily living routine were mostly interrupted as compared to when they were at home. The short-term IOP fluctuation may not be significantly manifested while in the ward. Furthermore, IOP measurement was taken in sitting upright position, abolishing habitual position during sleep time. This could mask the actual IOP reading and produce erroneous result as compared to measurement in supine position.

This study would be more interesting if normal population also was being recruited as control, in which more significant and reliable results may be produced in comparing normal and abnormal subjects especially in IOP variations analysis. Factors that may affect IOP fluctuation such as extent of peripheral anterior synechiae (PAS) also should have been explored, evaluated, and correlated.

At this point, issue of IOP fluctuation should be our main concern. The single IOP reading at achieved IOP target during regular clinic visit does not guarantee that the glaucoma progression has come to a halt. Ideally, more effective IOP stabilization may be achieved with surgical intervention, which is the glaucoma filtering surgery. As for the non-progressed PACG, they should be closely followed-up for a longer duration. Focusing on both reduction of mean IOP and IOP fluctuation should be the main agenda and targets. This group will definitely progress if we neglect either one of those. Maximum pharmacotherapy should be exercised to selected patients.

Maybe finally, glaucoma filtering surgery ought to be also considered in resistant cases.

Even though this study was limited with the previously discussed factors, it has provided a new insight to our clinical practice about 24-hour profile of IOP fluctuation in PACG patients.

5.2 Limitations and Recommendation

We highlighted several limitations in our study and the recommendations for future studies.

1. Due to small sample size, we had included both eyes. In the future, a larger sample size of one eye for each patient is recommended.

2. There is unequal number of samples for each group thus most of the data were skewed and nonparametric statistics were applied. This resulted in lower degree of confidence than if the results were obtained using parametric statistics. In the future, equal number of samples for each group is recommended so that normal distribution of data can be achieved.

3. There is no recruitment of normal population as control. In the future, matched control group is recommended.

3. In our study, patients need ward admission for 24-hour period. IOP measurements were taken with GAT in sitting position. This was likely affecting the IOP readings in our study, thus the result may not be as accurate as in patients' usual environment and habitual position. In the future, we recommend handheld mobile device such as ICare One tonometer for recording IOP and IOP monitoring at home. IOP measurements should be taken in habitual position with minimal interruption of activity daily living routine.

4. There was no washout period for patients that were on medications in this study. In the future, washout period prior to IOP measurements is recommended.

5. There was no evaluation of factors affecting IOP fluctuation such as peripheral anterior synechiae. In the future, factors affecting IOP fluctuation as above is recommended.

CHAPTER 6
CONCLUSION

6.0 CONCLUSION

1. In progressed PACG, the 24-hour median IOP was 13.7 mmHg, 24-hour IOP peak was 17.0 mmHg, 24-hour IOP trough was 11.0 mmHg, and 24-hour IOP fluctuation was 6.0 mmHg.

2. In non-progressed PACG, the 24-hour median IOP was 15.3 mmHg, 24-hour IOP peak was 18.0 mmHg, 24-hour IOP trough was 13.0 mmHg, and 24-hour IOP fluctuation was 6.0 mmHg.

3. There was no significant difference of 24-hour IOP, IOP peak, IOP trough, and IOP fluctuation between progressed and non-progressed PACG.

4. Circadian rhythm of IOP in progressed PACG showed patterns of night peak with afternoon trough, while non-progressed PACG exhibited patterns of afternoon peak with night trough. This was however not statistically significant.

CHAPTER 7
REFERENCES

7.0 REFERENCES

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CHAPTER 8
APPENDICES

APPENDIX A: Clinical Record Form

DEPARTMENT OF OPHTHALMOLOGY

SCHOOL OF MEDICAL SCIENCES, UNIVERSITI SAINS MALAYSIA

A. BIODATA OF PATIENT

1. Registration Number (RN) : _____
2. Phone number Home: _____
   Mobile:_____
3. Address _____
   _____
4. Date of birth _____
5. Age _____
6. Gender M / F
7. Ethnicity Malay / Chinese / Indian / Others: _____
8. Nationality Malaysian / Non-Malaysian (please state: _____)

B. **SYSTEMIC DISEASE**

a. Diabetes mellitus ☐
b. Hypertension ☐
c. Hypercholesterolemia ☐
d. Autoimmune disease ☐
e. Tuberculosis ☐
f. HIV/Hep B/Hep C ☐
g. Cancer ☐
h. Other diseases :

_____

C. OCULAR DISEASE (NON-GLAUCOMA)

OD	OS

D. DIAGNOSIS and EXAMINATION AT FIRST PRESENTATION

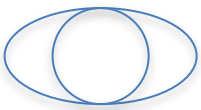
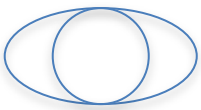
1.PACG Acute Non-acute

2. AGIS score _____

Mild ☐
Moderate ☐
Severe ☐
End-stage ☐

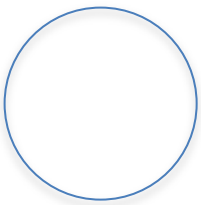
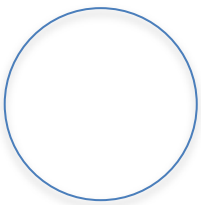
3. Visual Acuity OD ☐ OS ☐
ph ph

4. Anterior segment OD OS

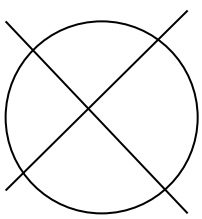
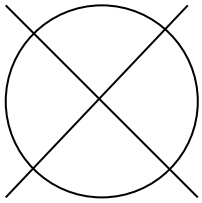



5. Intraocular pressure OD _____ OS _____

6.Posterior segment

7. Gonioscopy OD OS

8. Date of Diagnosis: _____
Duration of Glaucoma: _____

9. Visual Field: OD MD/PSD _____

OS MD/PSD_____

10. Number and type of topical antiglaucoma eye drops

OD	OS
1.	1.
2.	2.
3.	3.
4.	4.

10. Laser PI OD _____ OS _____

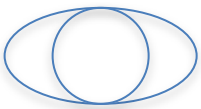
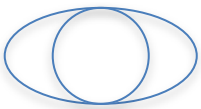
11. Cataract surgery OD☐_____ OS☐_____

E. EXAMINATION AT CURRENT PRESENTATION

1. AGIS score _____ Mild ☐
Moderate ☐
Severe ☐
End-stage ☐

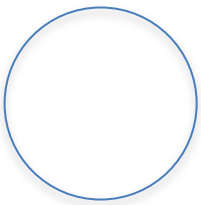
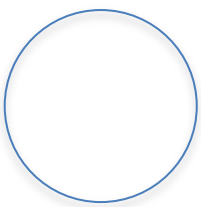
3. Visual Acuity OD ☐ OS ☐
ph ☐ ph ☐

4. Anterior segment OD OS

5. Intraocular pressure OD _____ OS _____

6.Posterior segment

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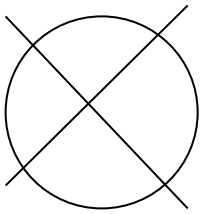
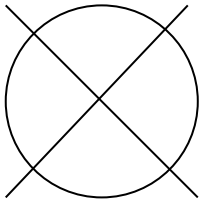



9. Visual Field: OD MD/PSD _____

OS MD/PSD_____

10. Number and type of topical antiglaucoma eye drops

OD	OS
1.	1.
2.	2.
3.	3.
4.	4.

11. Laser PI OD ☐_____ OS ☐_____

12. Cataract surgery OD ☐_____ OS ☐_____

13. OCT (RNFL analysis) OD _____ OS _____

14. CCT OD _____ OS _____

9. Fundus photo OD _____ OS _____

F. SYSTEMIC EXAMINATION

1. Weight
2. Height
3. BMI
4. BP

APPENDIX B: Patient Information Sheet

Patient Information Sheet and Consent Form

The Effect Of 24-Hour Intraocular Pressure Fluctuation On Glaucoma Progression In Primary Angle Closure Glaucoma

Researcher's Name: Dr. Haslinda A.Rahim @ Samsuddin
Supervisor's Name: Associate Professor Dr. Azhany Yaakub
Co Supervisor's Name: Professor Dr. Liza Sharmini Ahmad Tajudin

Introduction

You are invited to participate in a study on :

The Effect Of 24-Hour Intraocular Pressure Fluctuation On Glaucoma Progression In Primary Angle Closure Glaucoma.

Before you agree to take part, it is important that you read and understand about the information written on this sheet. It describes the purpose, procedure, benefit, side-effects and precautions about the study. It also explains about your right to withdraw yourself from this study at any stage of the study. If you agree, you will receive one copy of this information sheet for your reference. It is estimated that 56 patients will participate in this study. It will be carried out in Ophthalmology Clinic and Ophthalmology Ward (2 UTARA) Hospital Universiti Sains Malaysia; from May 2012 to May 2014.

Purpose of this study

The objective of this study is to determine and compare the pattern of IOP fluctuation in patients with primary angle closure glaucoma and its effect on glaucoma progression.

Any study related information that identifies you will remain confidential and will not be made publicly available. The data obtained will only be used for literature publication and scientific interest.

Qualification to Participate

The doctor in-charged or the staff in this study will discuss with you concerning the eligibility to participate in this study. It is therefore important for you to reveal the detail of your health and medical history accurately. The selection is based on the inclusion criteria as follow and you are not able to take part in the study if you do not fulfill all the following criteria;

1. Able to understand the nature of the study and willing to sign written consent form.

You are not eligible if you

1. Unable to understand the nature of the study and not willing to sign written consent form.

Study Procedures

First visit:

You will be approached if you are eligible for the study.

Second visit:

You will be admitted for 24 hours and 4 hourly IOP measurement will be taken.

Participation in this Study

Your participation in this study is entirely voluntary. You may refuse to take part in this study or you may stop your participation in this study at anytime, without penalty or loss of benefits to which you are otherwise entitled. Your participation may also be stopped by the study doctor without your consent.

Treatment and Compensation for Injury

If you follow the instruction, any physical injury as a result of the procedure that was given to you as required by the study, will be covered by the sponsors when it is not covered by the insurance, government programmes or other third party.

Possible Benefits

You may not have any direct benefit from the participation of the study. You may obtain information regarding your eye's health condition and laboratory test that may be provided in the study. However, your participation in this study will give us some information which might help us treat our future patients better.

Confidentiality

Your medical records will be kept confidential and will not be disclosed in public unless requested by the law. Data obtained from this study that does not identify you individually may be published. The original medical record may be seen by the ethical committee for certification of the procedure and clinical data. Your medical information may be held and processed on a computer.

Signature

By signing this consent form, you authorize the record review, information storage and data transfer. To take part in this study, you or your legal guardian must sign and date the consent form.

Should you have any question or doubt regarding this study or concerning you rights, please contact

1. Dr Haslinda A.Rahim @ Samsuddin (012-8081775)

Borang maklumat dan keizinan peserta

Kajian Dua Puluh Empat Jam Turun Naik Tekanan Intraokular Ke Atas Kemajuan Glaucoma Di Kalangan Pesakit Glaukoma Primer Sudut Tertutup.

Nama Penyelidik: Dr. Haslinda A.Rahim @ Samsuddin
Nama Penyelia: Associate Professor Dr. Azhany Yaakub
Nama Penyelia Bersama: Professor Dr. Liza Sharmini Ahmad Tajudin

Pengenalan
Anda dipelawa untuk menyertai satu kajian penyelidikan secara sukarela yang melibatkan pengukuran tekanan intraokular dalam masa 24 jam. Sebelum anda bersetuju untuk menyertai kajian penyelidikan ini, adalah penting anda membaca dan memahami tentang apa yang ditulis di dalam borang ini. Borang ini akan menghuraikan tujuan, prosedur, manfaat, risiko , ketidakselesaan dan langkah berjaga-jaga kajian ini. Ia juga menghuraikan hak anda untuk menarik diri dari kajian ini pada bila-bila masa. Sekiranya anda menyertai kajian ini, anda akan menerima satu salinan borang ini untuk disimpan sebagai rekod anda.

Tujuan Kajian
Kajian ini bertujuan untuk menentukan corak turun naik tekanan intraokular dalam masa 24 jam dan kesannya ke atas kemajuan glaucoma. Segala maklumat yang diperolehi daripada anda akan dirahsiakan oleh kami. Semua data yang diperolehi daripada anda hanya akan digunakan untuk penulisan ilmiah dan pembentangan kertas-kertas saitifik. Data yang diperolehi adalah dianggap SULIT.

Kelayakan Penyertaan
Doktor yang bertanggungjawab dalam kajian ini atau salah seorang kakitangan kajian telah membincangkan kelayakan untuk menyertai kajian ini dengan anda. Adalah penting anda berterus terang dengan doktor dan kakitangan tersebut tentang sejarah kesihatan anda. Anda tidak seharusnya menyertai kajian ini sekiranya anda tidak memenuhi semua syarat kelayakan.
Keperluan untuk menyertai kajian ini adalah :
1.Anda faham tentang kajian ini dan setuju untuk menandatangi surat keizinan

Anda tidak boleh menyertai kajian ini sekiranya :
1.Anda tidak faham tentang kajian ini dan tidak bersetuju untuk menandatangani surat keizinan

Prosedur-prosedur Kajian
Lawatan pertama
Anda akan dipelawa untuk menyertai kajian ini sekiranya anda didapati layak.
Lawatan kedua
Anda akan dimasukkan ke wad selama 24 jam dan setiap 4 jam tekanan intraocular akan direkodkan.

Penyertaan Dalam Kajian

Penyertaan anda dalam kajian ini adalah secara sukarela. Anda boleh menolak penyertaan dalam kajian ini atau anda boleh menamatkan penyertaan anda dalam kajian ini pada bila-bila masa, tanpa sebarang hukuman atau kehilangan sebarang manfaat yang sepatutnya diperolehi oleh anda. Keputusan anda akan diterima tanpa sebarang prasangka.

Penyertaan anda mungkin juga diberhentikan oleh doktor kajian tanpa persetujuaan anda sepertimana dinyatakan sebelum ini.

Jika anda berhenti menyertai kajian ini, doktor kajian atau salah seorang kakitangan akan berbincang dengan anda mengenai apa-apa isu perubatan berkenaan dengan pemberhentian penyertaan anda.

Manfaat yang Mungkin

Ubat dan prosedur kajian akan diberikan kepada anda tanpa kos. Anda mungkin menerima maklumat tentang kesihatan anda dari apa-apa pemeriksaan fizikal dan ujian makmal yang bakal dilakukan dalam kajian ini.

Maklumat yang didapati mungkin memanfaatkan pesakit pada masa depan.

Sekiranya anda mempunyai sebarang soalan mengenai kajian ini atau hak-hak anda, sila hubungi

- Dr Haslinda Binti A.Rahim @ Samsuddin (012-8081775)

APPENDIX C: Consent Form

Patient Information and Consent Form (Signature Page)

Research Title : The Effect Of 24-Hour Intraocular Pressure Fluctuation On Glaucoma Progression In Primary Angle Closure Glaucoma

Researcher's Name: Dr. Haslinda A.Rahim @ Samsuddin
Supervisor's Name: Associate Professor Dr. Azhany Yaakub
Co Supervisor's Name: Professor Dr. Liza Sharmini Ahmad Tajudin

To become a part this study, you or your legal representative must sign this page.

By signing this page, I am confirming the following:

1. I have read all of the information in this Patient Information and Consent Form including any information regarding the risk in this study and I have had time to think about it.
2. All of my questions have been answered to my satisfaction.
3. I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
4. I may freely choose to stop being a part of this study at anytime.
5. I have received a copy of this Patient Information and Consent Form to keep for myself.

_____ _____
(Patient's signature) Date
Patient's name:
IC number:

_____ _____
Signature of legal guardian Date
Name:
IC number:

_____ _____
Signature and name of investigator Date
Name:
IC number:

_____ _____
Signature of witness Date
Name:
IC number:

Borang Maklumat dan Keizinan Pesakit (Halaman Tandatangan)

Untuk menyertai kajian ini, anda atau wakil sah anda mesti menandatangani mukasurat ini.

Dengan menandatangani mukasurat ini, saya mengesahkan yang berikut:

- Saya telah membaca semua maklumat dalam Borang Maklumat dan Keizinan Pesakit ini, dan saya telah diberi masa yang mencukupi untuk mempertimbangkan maklumat tersebut.
- Semua kemusykilan saya telah dijawab dengan jawapan yang memuaskan.
- Saya, secara sukarela, bersetuju menyertai kajian penyelidikan ini, mematuhi segala prosedur kajian dan memberi maklumat yang diperlukan kepada doktor, para jururawat and juga kakitangan lain yang berkaitan apabila diminta.
- Saya boleh menamatkan penyertaan saya dalam kajian ini pada bila-bila masa.
- Saya telah menerima satu salinan Borang Maklumat dan Keizinan Pesakit untuk simpanan peribadi saya.

_____ _____

Tandatangan Pesakit Tarikh

Nama Pesakit:

No. Kad Pengenalan:

_____ _____

Tandatangan Wakil Sah Pesakit Tarikh

Nama:

No. Kad Pengenalan:

_____ _____

Tandatangan Individu yang Mengendalikan Perbincangan Keizinan (Ditera atau Ditaip) Tarikh

Nama:

No. Kad Pengenalan:

_____ _____

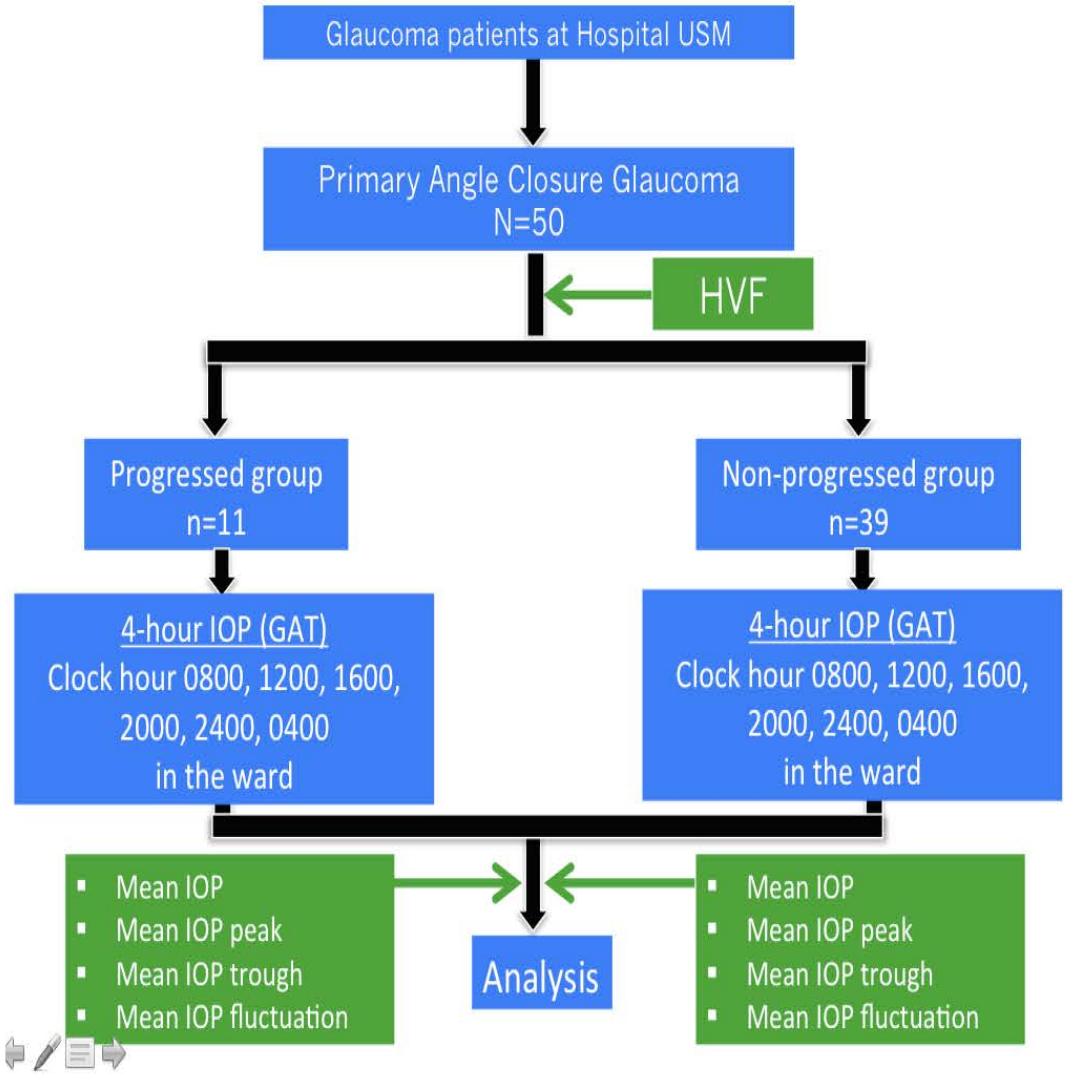
Tandatangan Saksi Tarikh

Nama:

No. Kad Pengenalan:

(AGIS score)

APPENDIX D: Flow Chart of Methodology



JOURNAL OF PUBLICATIONS

2010-2015

By

Dr. Haslinda A.Rahim @ Samsuddin

MD (USM)

P-UM 0040/10

Journal Publications Submitted In Partial Fulfillment

Of The Requirement For The Degree Of

Master Of Medicine (OPHTHALMOLOGY)

SCHOOL OF MEDICAL SCIENCES

UNIVERSITI SAINS MALAYSIA

2015

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I would also like to thank my colleagues and staffs of the Department of Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia, for their kind assistance in helping me along my journey throughout my course.

Last but not least, I would like to extend my heartfelt thanks to my parents, Encik Samsuddin @ A.Rahim Mohd Ali and Puan Wan Hasenah Wan Ahmad for their endless prayers and unwavering faith in me. I dedicate this effort to my spouse, Encik Ahmad Zaky Mokhtar and my two children, Aisyah Amellin and Adam Anaqi who were the source of joy and strength in the completion of this work.

TABLE OF CONTENTS

PUBLICATION 1

Lateral rectus myositis mimicking an abducens nerve palsy in a pregnant woman.

Ophthalmic Plastic Reconstructive Surgery, 30(1), e13-15.

Lateral Rectus Myositis Mimicking an Abducens Nerve Palsy in a Pregnant Woman

Abd-Rahim Haslinda, M.D., Ismail Shatriah, M.Med.*, Yaakub Azhany, M.Med.*, Nik-Lah Nik-Ahmad-Zuky, M.Med.†, and Rohaizan Yunus, M.Med.‡*

Abstract: **Myositis is a rare unknown inflammatory disorder of the skeletal muscle tissue. Generalized inflammatory myopathies, polymyositis, and dermatomyositis have been reported during pregnancy. Isolated orbital myositis in pregnancy has not been previously described in the literature. The authors report a case of left isolated orbital myositis in a primigravida at 38 weeks gestation affecting the patient's left lateral rectus muscle. MRI of the orbit was consistent with the diagnosis. She showed remarkable clinical improvement with oral corticosteroids therapy.**

A sudden onset of esodeviation in late pregnancy is an alarming situation. Palsy of the abducens nerve is the most common cause reported in pregnant women.[1–10] This condition has been caused by preeclampsia,[1–3] spinal anesthesia,[4–6] postfebrile illness,[7] intracranial pathology,[8] and unknown etiologies.[9,10] The authors report a case of a mimicking left abducens nerve palsy in a primigravida, which was subsequently diagnosed as lateral rectus myositis.

There are no known cases of isolated myositis during pregnancy reported in the literature. Generalized forms of skeletal muscle inflammation, such as generalized inflammatory myopathies, polymyositis, and dermatomyositis, have been reported in pregnancy.[11–14] Thus, it is essential that ophthalmologists and obstetricians be informed regarding this uncommon presentation in pregnant women. The report adhered to the tenets of the Declaration of Helsinki.

CASE REPORT

A 30-year-old primigravida at 38 weeks of gestation sought treatment for a sudden onset of painful diplopia for 3 days. The patient expressed no history of blurred vision, fluctuating eye symptoms, proptosis, or ptosis. She denied previous trauma, flu-like illness, neck swelling, or symptoms suggestive of increased intracranial pathology. She had experienced no similar illness previously, and her pregnancy was uneventful.

The visual acuity was 6/6 in OU. There was a left esodeviation of 30 prism diopters with an abduction deficit in the corresponding eye. The other ocular motility was within the normal range (Fig. 1). There was no eyelid retraction or eyelid lag, and no relative pupillary defect was noted. The examinations of the anterior and posterior segments were normal. There was no sign of orbital or ocular inflammation. The optic disk was pink, with a well-defined margin in OU. The intraocular pressure was normal bilaterally.

The patient was comfortable and cooperative during a systemic examination. Her blood pressure was 120/78 mm Hg, and pulse rate was 84 beats/minute. Her other cranial nerves were found to be intact with no neurological deficit either the upper or lower limbs. An abdominal examination revealed a gravid uterus that corresponded with the period of gestation. A singleton longitudinal lie of fetus was noted.

The full blood picture of the patient was within the normal range, and the white cell count was $9.02 \times 10^3/\mu l$. The erythrocyte sediment rate was moderately raised to 50 mm/hour. The fasting blood sugar, thyroid function test, renal function test, liver function test, double-stranded deoxyribonucleic acid, and acetylcholine receptor antibodies were normal. A repetitive nerve conduction test was negative. The MRI of the orbit revealed a slightly enlarged left lateral rectus with a normal-appearing anterior muscle tendon (Fig. 2). The brain MRI was otherwise normal.

The patient was referred to a neurophysician and obstetrician for proper evaluation. Oral corticosteroids at a dose of 1.0 mg/kg/day were started with close monitoring for potential side effects. The ocular pain subsided, and her left abduction motility showed remarkable improvement after 1 week of treatment. She tolerated the medications well.

The patient had an induced vaginal delivery at 40 weeks of gestation and delivered a healthy normal baby girl with a birth weight of 2.8 kg. The oral corticosteroid was tapered gradually and terminated after a duration of 6 weeks. The diplopia had resolved completely, and she remained orthophoric with a full left abduction during her postnatal period.

The patient was last seen at 6 months after the delivery. No symptoms of relapse were noted during the follow-up visits. No significant complications related to steroid use were observed throughout the post-therapy period.

DISCUSSION

Idiopathic orbital myositis is an uncommon disease. It is a subtype of nonspecific orbital inflammatory disease, and its occurrence during or immediately after pregnancy is extremely rare. A PubMed search revealed 2 cases of orbital myositis that developed after pregnancy.[15,16] The case described here is interesting because she sought treatment for an attack of left lateral rectus myositis at the end of her pregnancy.

There is no clear pathogenesis of orbital myositis occurrence during pregnancy. However, it is known that pregnancy affects hormonal changes and plays a major role in modulating certain diseases, especially autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). SLE is an immune-mediated pathology linked to excess Th2 production, and it usually flares up during pregnancy, whereas RA is a cell-mediated immunopathology that is linked to a deficiency in Th2 cytokine production. RA commonly remits during pregnancy and flares up or initially develops in the postpartum period. Wilder[17] reported that during pregnancy, the cell-mediated immune function and Th1 cytokine productions are suppressed and humoral immunity and Th2 cytokine production are enhanced. These patterns are reversed in the postpartum period.[17]

The diagnosis of the case described here was mainly based on clinical and imaging evidences. The authors did not perform a muscle biopsy to confirm the histopathologic diagnosis. Her delivery and postnatal periods were uneventful. Extensive investigations were performed to identify any

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DOI: 10.1097/IOP.0b013e31828957ae

FIG. 1. Clinical photographs showing limited left abduction.

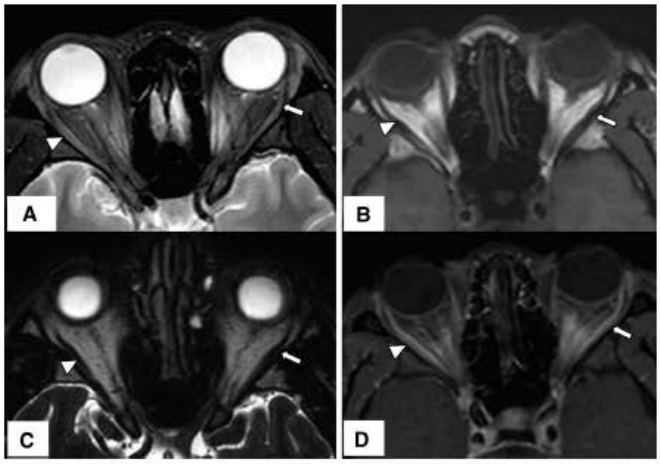

FIG. 2. Axial images of MR (**A**, T2 with fat suppression; **B**, T1WI; **C**, Axial MPR T2 3D DRIVE; **D**, postgadolinium T1W with fat suppression). The *block arrow* shows subtle swelling of the belly of the left lateral rectus, a change in signal intensity, and minimal enhancement compared with the right lateral rectus muscle (*arrowhead*). The left retrobulbar fat shows enhancement compared with the right side (**D**). Corresponding images of the left lateral rectus myositis.

possible etiology of myositis in the authors' patient. She was monitored closely due to the possibility of relapse. The authors' patient was treated with oral corticosteroids for 2 weeks during her late pregnancy and for 4 weeks in the postpartum period. Dramatic improvement of orbital myositis after delivery with corticosteroid treatment has also been described by Hiraga et al.[15] However, Mombaerts and Koornneef[16] did not specify the details in their case series.

Corticosteroids treatment at a dose up to 15 mg/day is generally safe during pregnancy.[18] However, higher doses of corticosteroids increase the risk of maternal infection and premature delivery.[19] Corticosteroids are also considered safe during lactation. Prednisolone is secreted into the breast milk at estimated doses of less than 0.1% of the maternal dose, and it is thought that this level is less than 10% of the endogenous cortisol level in the infant.[20]

In conclusion, it is important to highlight this misleading ocular presentation in pregnant women when it occurs close to the delivery phase. Prompt diagnosis and management are vital. Long-term follow up is necessary to monitor relapse, especially in subsequent pregnancies.

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PUBLICATION 2

Cyanoacrylate tissue glue for wound repair in early conjunctival bleb leak post trabeculectomy: a case series.

(Submission aaccepted for publication in *"International Medical Case Reports Journal"*)

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83821

Cyanoacrylate Tissue Glue for Wound Repair in Early Conjunctival Bleb Leak Post Trabeculectomy: A Case Series

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Abstract

We demonstrated a non-invasive management of early bleb leak following trabeculectomy using cyanoacrylate tissue glue (CATG). Three patients who underwent augmented trabeculectomy with mitomycin C with early bleb leak between January 2009 to June 2010 were reviewed. Case 1 and case 2 were noted bleb leak at postoperative day 1 and case 3 was noted leak on follow up at postoperative day 7. Case 1 was successfully sealed with CATG at postoperative day 3, after failed pressure padding and bandage contact lens . Case 2 was successfully sealed with CATG at postoperative day 3, after failed pressure padding and conjunctiva flap resuturing. In case 3, the leakage conjunctival flap was managed with combined techniques of resuturing and applying CATG at postoperative day 9, after failed pressure padding. During leakage, the intraocular pressure was low (6-8 mmHg) in all three cases with shallow anterior chamber depth, and absence of other complications such as choroidal detachment, hypotony maculopathy or endophthalmitis. Foreign body sensation was the main complaint following the procedure. No clinical allergy reaction was documented. CATG may serve as one of the potential adjunctive and effective methods in the management of post-trabeculectomy with early bleb leak.

Key words: cyanoacrylate tissue glue, bleb leak, trabeculectomy, mitomycin C

Introduction

Trabeculectomy is a surgical glaucoma procedure that aims to lower the intraocular pressure (IOP) by creating a fistula for aqueous drainage from anterior chamber to subtenon space. Lower IOP will prevent further insult to the optic nerve and hence further visual field loss. Mitomycin C (MMC) is commonly used as adjunctive treatment in trabeculectomy in order to increase the survival of filtering bleb. However, MMC also increases the incidence of bleb leak. Bleb leakage that occurs within the first 1 month following trabeculectomy is considered an early postoperative leak, and it is frequently encountered as unfortunate complication.[1] Its incidence varies from 0% to 30%.[2] The bleb leak may be self-limiting or complicated with shallow and flat anterior

chamber, cataract formation, choroidal detachment and hypotony maculopathy. [3] Risk of bleb-related infection increases up to 26 folds following bleb leakage.[4]

Conservative measures and medical approaches have been practiced prior to consideration of surgical retreatment in bleb leak cases. These include pressure patching, bandage soft contact lens, collagen shield, sclera shell tamponade, aqueous suppressants, compression suture, conjunctiva suturing, trichloroacetic acid, and autologous blood injection.[5] For decades, surgical repair or wound revision has been a gold standard in management of leaking bleb. Until recently, application of tissue adhesive has been widely accepted as suture alternative. The use of cyanoacrylate tissue glue (CATG) has been successfully reported in ophthalmology literatures; from sealing corneal perforations to closure of retinal breaks and reattachment of retina in retinal detachment cases.[6]

Cyanoacrylate belongs to a family of polymer. Liquid form of cyanoacrylate consists of monomers of cyanoacrylate molecules, clear colourless appearance with strong odour. The ester form of cyanoacrylate, N-butyl cyanoacrylate, is one of the adhesive components which have been widely used in medical and veterinary applications.[7] Cyanoacrylate liquid monomers rapidly solidify by polymerization and form a firm adhesive bond when coming into contact with weak base released by little heat, as well as in presence of ionic substances like moisture, blood or tissue fluids.[7] In polymerized form, its tensile strength of bonding has been observed as the highest among all glues. It also has bacteriostatic property.[8] Another alternative of adhesives available include biological fibrin glue; a blood-derived product gelatin and thrombin products, albumin and glutaraldehyde products, as well as polyethylene glycol polymers.[9]

We reported 3 successfully sealed early bleb leak cases with CATG. We have used GluStitch®, an N-Butyl-2-cyanoacrylate tissue adhesive type.

Case series

We retrospectively analyzed the outcome of three patients with early leaking filtering blebs managed with cyanoacrylate tissue glue. We reviewed the medical records of 3 patients who underwent augmented trabeculectomy with MMC with early bleb leak between January 2009 and June 2010. All patients gave informed consent and their anonymity was preserved.

Two cases had bleb leakage at day 1 postoperative, and one case had detected bleb leakage at day 7 postoperative. The diagnosis of bleb leaks was confirmed by a positive Seidel's test, which also identified the leakage site. All bleb leakage was less than 2 mm size. They occurred either from conjunctival flap buttonhole or along suture track, which located more than 2 mm from limbus. The leak was complicated with low IOP of less than 10 mmHg, shallow anterior chamber depth but without iridocorneal touch. Other complications such as choroidal detachment, hypotony maculopathy or endophthalmitis were absent in all cases. The patients retained their preoperative visual acuity.

An individualised approach was used in every case. The first line of management was conservative which consisted of pressure padding, bandaged contact lens, and aqueous suppression. In first case, CATG was used along with plastic disc after 2 days failed pressure bandage. In second case, CATG was used alone after 2 days failed conservative method and subsequent surgical procedure. While in third case, CATG was used in combination with surgical procedure after 2 days failed pressure bandage. Summary of cases and outcome was shown in Table 1.

All patients underwent application of CATG under topical anesthesia of proparacaine 0.5% or subconjunctiva lignocaine 2%. To facilitate instillation of CATG, 0.1 ml of CATG was filled in 1 ml tuberculin syringe mounted with 30 G needle. A drop of CATG was approximately equivalent to 0.05 ml. Plastic disc was used in one of the cases (case 1). It was a modified disc of 4 mm diameter, cut from sterile soft clear plastic cover of butterfly needle, using straight scissors. The leakage sites were dried using dry cotton applicator.

Post-gluing, they received topical eyedrops of prednisolone acetate 1% 4 hourly per day, ciprofoxacin 2 hourly per day, and homatropine 1% twice daily for 2 weeks. At 2 weeks, both prednisilone acetate 1% and ciprofloxacin were tapered to four times per day for another 2 weeks while homatropine was stopped. At 4 weeks, ciprofloxacin was stopped and prednisolone acetate 1% was used four times daily for further 2 to 3 months. Patients were followed-up weekly after gluing for 1 month, then subsequent monthly review. During clinic visits, blebs were diffusely formed with no recurrent leak in all cases. No incidence of blebitis or endophthalmitis at 3 months follow-up.

Case 1

A 57-year-old male with right eye neovascular glaucoma secondary to branch retinal vein occlusion underwent right eye augmented trabeculectomy. He developed filtering bleb leak on day 1 postoperative period. On ocular examination, there was presence of shallow bleb with positive Seidel test was seen at nasal part of the bleb. The anterior chamber was shallow and intraocular pressure (IOP) with applanation tonometry was 8 mmHg. The eye was managed with pressure padding and bandaged contact lens for 2 days. Examination on following day revealed persistent slow bleb leak from similar site (Figure 1). Sealing of the leaking bleb with CATG with plastic disc was done at postoperative day 3 under slit lamp. Patient was first seated, and then the identified bleb leakage site was dried. One drop of CATG was applied (Figure 2), and a plastic disc was placed on top (Figure 3). It was allowed to crystallize for 5 minutes. The site was again checked with fluorescein sodium strip, and no sign of leakage was observed (Figure 4). Eye examination on day 1 post-gluing showed negative Seidel test, clear cornea, anterior chamber deepened with IOP 18 mmHg. He complained of mild foreign body sensation post-gluing. Two weeks later the plastic disc glue was self-dislodged with no subsequent ocular complication. Follow up at 3 months showed well sealed bleb, no recurrent leak with IOP of 19 mmHg.

Case 2

A 63-year-old male underwent left eye augmented trabeculectomy surgery in January 2009 for refractory secondary glaucoma after failed initial non-augmented trabeculectomy. He developed

filtering bleb leak on day 1 postoperative period. On ocular examination, there was presence of shallow bleb with positive Seidel test was seen at temporal part of bleb. The anterior chamber was shallow and IOP with applanation tonometry was 6 mmHg. The eye was managed with pressure padding and aqueous suppression. The next day, there was persistent leaking. Conjunctival flap resuturing was performed. On day 3 postoperative, the bleb showed leakage again from the similar site with IOP 7 mmHg. Sealing of the leaking bleb with CATG was done on the same day. As the patient was laid supine, an eye speculum was placed to prevent blinking. The identified leakage site was then dried. One drop of CATG applied, and left to crystallize for 5 minutes. The glued site was checked with fluorescein strip, and no sign of leakage observed. Eye examination on day 1 post-gluing revealed negative Seidel test, clear cornea, and anterior chamber deepened with IOP 12 mmHg. He complained of mild foreign body sensation for subsequent 1 week, which was tolerable with minimal irritation. The last follow up was at 3 months post procedure whereby the filtering bleb was Siedels' negative and IOP maintained below 15 mmHg. Patient was then defaulted to follow up.

Case 3

An 81-year-old female, a case of both eyes advanced primary open angle glaucoma underwent left eye augmented trabeculectomy in March 2009. She developed filtering bleb leak on day 7 postoperative period. On ocular examination, there was presence of bleb leak with positive Seidel test near the limbus. The anterior chamber was shallow and IOP with applanation tonometry was undetectable. The eye was managed with pressure padding for 2 days. Examination on following day revealed persistent slow bleb leak from similar site. As the bleb was persistently leaked, she underwent combined techniques of resuturing and applying CATG at postoperative day 10. In supine position, eye speculum was placed. The identified leakage site of conjunctival flap was first resutured. The site was then dried. One drop of CATG was applied, and it was left to crystallize for 5 minutes. The sutured and glued site was checked with fluorescein strip, and there was no sign of leakage observed. Eye examination on day 1 post-gluing noted Seidel test was negative, cornea was clear, anterior chamber deepened with IOP 10 mmHg. There was complaint of mild foreign body sensation post-gluing for 3 weeks, however no

severe irritation noted. At 3 months follow up, the bleb remained Siedel's negative with the IOP slightly increased to 15 mmHg.

Discussion

Managing the bleb leaks often set a challenge upon failing both conservative approach and surgical repair. The incidence of postoperative bleb leakage after trabeculectomy was reported to reach up to 56%,[10] in which higher risk was anticipated with the use of augmenting metabolites.[11] The widely use of MMC as adjunctive during trabeculectomy was found to be a cause for delayed bleb leaks.[12] Meanwhile, early bleb leaks which comprise of wound leak and conjunctiva buttonholes are likely to be contributed by fluctuation changes in tissue swelling during postoperative period, cutting through of sutures or changes in wound apposition caused by blinking or eye rubbing; apart from deficient wound closure, patent stitch tracts and surgically traumatized conjunctiva.[13]

Despite that, early bleb leak is not a poor prognostic indicator for intermediate bleb survival and IOP control in patients undergoing MMC trabeculectomy as proved by Alwitry and his team.[1] Longer follow-up of more than 1 year is necessary to futher determine relationship between early bleb leak and long term bleb survival.

Cyanoacrylate use in managing bleb leaks and the glue has the advantage of biocompatibility that allows application over ocular surface with minimal toxicity while promoting and facilitating rapid re-epithelialization.[14] Successful closure of leaking blebs with cyanoacrylate adhesive in studied cases were achieved either using the glue alone or in combination with other conservative methods, such as pressure patching, bandage soft contact lens, Simmon's shell, aqeous suppressant, autologous blood, and dye-enhanced argon laser photocoagulation.[15-17] Several applications of the tissue adhesives though, may be required to ensure favorable outcome, as reported by Okabe and his colleagues.[18] However, unsuccessful result also being

reported with the tissue glue. Mandal attempted cyanoacrylate in 4 out of 7 cases with late bleb leak but found them unsuccessful.[19]

There were significant differences between their studies and our study. Most of the previous reported bleb leaks were late-onset occurrence, and majority did not specify the size of the leak. In our cases, all three were detected very early within a week post-trabeculectomy, which was augmented with MMC. This is in agreement with the study conducted by Alwitry and his team, which found that the time of detection of early bleb leak range 1 to 21 days in MMC trabeculectomy patients.[1] The size of leak was small in all of our cases, permitting the use of CATG.

There was no impending vision-threatening complication set in upon the onset. We considered premature intervention without hypotony maculopathy or choroidal detachment was reasonable after adequate trial of conservative postoperative care having been undertaken. Cyanoacrylate adhesive was not our first line of bleb leak management though. The glue was attempted after failed initial conservative and/or surgical method in all of our cases. From our 3 cases, it seemed that the CATG was responsible in sealing the bleb leaks. However, we admitted that we were not too certain that the glue alone contributed to the effective seal of the bleb leaks as many of early leaks seal spontaneously. In more complicated of case 3 where gluing was undertaken but in combination with resuturing, again the success cannot be attributed solely to the glue.

From comparison of literature review and our cases, we observed that CATG could effectively be used as adjunct, rather than primary treatment to seal an early bleb leak of size 2 mm or less. CATG is not apparently suitable for thin avascular bleb with late-developing leaks. Case summaries of literature review were illustrated in Table 2.

The advantages of CATG in the management of early bleb leakage in our cases are as follows: (1) clinically no toxic effect on vascular tissue (2) strong and rapid bonding (3) good adherence to conjunctiva (4) ability to bond in the presence of small amount of blood and tears (5) possible

bacteriotoxicity (6) water tight, sutureless closure (7) accessible, affordable, fast, safe, simple and relatively ease of application.

There are few insignificant limitations over its use that have been addressed: (1) big pre-sterilized glue container tip making it difficult to specify and localize to the desired site (2) too liquify properties causing it to diffuse to other undesired surrounding site while waiting it to solidify (3) forming solid, impermeable mass in situ which persist as a foreign body, thus giving rise to foreign body sensation (4) impermeable to fluids and metabolites (5) risk of development of severe peri-bleb inflammation around both the glue and the plastic disc in the weeks after gluing, before the glue ultimately naturally dislodges.

Conclusion

CATG may serve as one of the effective alternative adjunctive method in the management of post-trabeculectomy early bleb leak. Nevertheless, further study of its use in various phases of bleb leak is required. Modification of product preparation of CATG for ophthalmic use will facilitate the usage.

Disclosure

The authors reported no conflict of interest for this article.

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Table 1: Summary of cases and outcome

Case	Age, Gender, Type of Glaucoma	Onset of bleb leak	Initial failed methods	Application method of CATG Time of treatment	IOP during bleb leak (mmHg)	IOP post gluing (mmHg)	Outcome
1	57 y/o, M , NVG	Post op Day 1	Pressure padding Bandage contact lens	CATG with plastic disc Post op Day 3	8	18	Success
2	63 y/o, M, NVG	Post op Day 1	Pressure padding Aqueous suppression Resuturing	CATG alone Post Op Day 3	7	12	Success
3	81 y/o, F, POAG	Post op Day 7	Pressure padding	CATG with resuturing Post op Day 10	undetectable	10	Success

Abbreviation: M, Male; F, Female; CATG, cyanoacrylate tissue glue; NVG, neovascular glaucoma; POAG, primary open angle glaucoma; IOP, intraocular pressure; op, operation.

Table 2: Case summaries of literature review

Author	Total	Onset of bleb leak	Management of bleb leak							Complications observed
			CATG alone			Combine CATG & other methods			Other methods	
			Total	Success	Fail	Total	Success	Fail	Total	
Zalta & Wieder[15]	5*	10 month – 20 year	1	1	0	4	4	0	-	corneal abrasion
Wilensky[16]	12*	6 month – 20 year	-	-	-	2	2	0	10[α]	N/A
Euswas et al[17]	7*	Late onset	-	-	-	2	2	0	5[α]	N/A
Okabe et al[18]	2*	Late onset	-	-	-	2	2	0	-	N/A
Mandal[19]	7*	1.5 year – 16 year	-	-	-	4	0	4	7[α]	N/A
Our series	3*	< 2 week	1	1	0	2	2	0	-	foreign body sensation

*cases managed with glue were included, [α]other methods of management of bleb leak also included, N/A – not available

Figure legend

Figure 1: Leaking bleb with Siedel's test positive (arrow) in case 1.

Figure 2: Application of cyanoacrylate tissue glue (arrow) in case 1.

Figure 3: Plastic disc applied on top of cyanoacrylate tissue glue (arrow) case 1.

Figure 4: Sealed leaking bleb with Siedel's negative. Plastic disc in situ (arrow) surrounded by crystalized cyanoacrylate tissue glue in case 1.